The New England
Journal of Medicine

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VOLUME 223 NOVEMBER 28, 1940 NUMBER 22

SULFATHIAZOLE THERAPY OF *STAPHYLOCOCCUS AUREUS* BACTEREMIA*

CHARLES H. RAMMELKAMP, M.D.,† AND CHESTER S. KEEFER, M.D.‡

BOSTON

STAPHYLOCOCCUS AUREUS bacteremia is always a grave disease. The mortality reported in large series of cases varies from 68 per cent[1] to 89 per cent.[2] Recently Mendell[3] reported 35 cases, with a fatality rate of 83 per cent, and Skinner and Keefer[4] found a mortality rate of 82 per cent in the study of 122 cases observed at the Boston City Hospital. These reports, which are based on large numbers of cases, serve to emphasize the need for a new therapeutic approach to this disease.

With the introduction of the thiazole derivatives of sulfanilamide by Fosbinder and Walter,[5] it soon became evident that these drugs would prove useful in the treatment of infections. Recent studies have shown that the thiazole derivatives inhibited the growth of *Staph. aureus* in broth[6, 7] and in urine.[8] Rammelkamp and Keefer[9] showed that when sulfathiazole was added to defibrinated whole blood in vitro there was a marked increase in the bactericidal and bacteriostatic action against pathogenic staphylococci. Further, it was determined that a concentration of between 2.5 and 5 mg. per 100 cc. of blood was necessary to obtain the maximal effect. Comparison of the bactericidal action of sulfathiazole, sulfamethylthiazole, sulfapyridine and sulfanilamide against *Staph. aureus* showed sulfathiazole to be slightly superior to the other drugs named. In experimental staphylococcal infections in mice, sulfathiazole prolongs the life of the animal.[10, 11]

Recently several cases of *Staph. aureus* bacteremia in which the patient recovered following treatment with sulfathiazole or sulfamethylthiazole have been reported.[12–15] These reports are encouraging, but to evaluate the effectiveness of sulfathiazole therapy in the treatment of staphylococcal bacteremia, it is necessary to analyze both successes and failures. For this reason the following study of 7 cases of *Staph. aureus* bacteremia treated with sulfathiazole§ is reported. In addition an investigation was made of the bactericidal properties of the blood obtained from 3 of these patients and from normal persons following the administration of sulfathiazole by mouth.

CASE REPORTS

CASE 1 (*Bacteremia with death*). A 62-year-old, married woman complained of cough and pain in the right chest. About a month before admission to the hospital she developed a cough that was productive of small amounts of cream-colored sputum. The cough gradually decreased up to the time of admission. Three days before entry she developed a "dagger-like" pain in the right chest that radiated to the precordium. This pain was constant, and it was aggravated by motion, deep breathing and coughing. There was no history of chills or previous staphylococcal infection. For several years she had experienced some dyspnea on exertion. There had been no recent weight loss or symptoms referable to the urinary tract.

On admission the temperature was 100.4°F., the pulse 84 and the respirations 24. The patient was overweight, but she did not appear acutely ill. The skin was dry and clean. The pharynx was not injected. In the lower jaw a few carious teeth were noted. The tongue was smooth and moist. Ophthalmoscopic examination revealed nothing abnormal. There was no lymphadenopathy. Chest expansion was good. On percussion there was dullness over the right lower lobe posteriorly, and over this area a few rales could be heard. The heart was not enlarged, and the sounds were of good quality. The blood pressure was 146/74. Examination of the abdomen revealed nothing abnormal. The reflexes were physiologic.

Laboratory examinations showed the urine to be clear and normal. The hemoglobin was 76 per cent, the red-cell count 3,960,000, and the white-cell count 18,000. A blood Hinton test was negative, the nonprotein nitrogen 22 mg. per 100 cc. Examination of the sputum failed to reveal any pneumococci. An x-ray film of the chest on admission showed some infiltration of the right lower lobe.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

†Assistant in medicine, Boston University School of Medicine; resident physician, Evans Memorial, Massachusetts Memorial Hospitals.

‡Assistant in medicine, Boston University School of Medicine; director, Evans Memorial, and physician-in-chief, Massachusetts Memorial Hospitals.

§We are indebted to Dr. George Harrop, of E. R. Squibb and Sons, New York City, for generous supplies of sulfathiazole.

The clinical course of this patient's illness is shown in Figure 1. At first, it was thought that the patient had a pneumonic process in the right lower lobe, and therefore she was given sulfapyridine. The blood culture taken on the day after admission was positive for *Staph. aureus.* After 1 week of fever the temperature returned to normal and the sulfapyridine was discontinued. Nevertheless, the blood continued to show *Staph. aureus* on culture. Sulfapyridine therapy was then resumed. Investigation as to the cause of the bacteremia failed to reveal a focus other than the pulmonary infiltration. X-ray films of the spine, pelvis and gall bladder and an intravenous pyelogram were interpreted as normal. At the end of the 4th week in the hospital the patient again had fever, and at this time sulfathiazole was started. During the first 3 days of this therapy the blood remained sterile, then again became positive. Because of nausea and failure to sterilize the blood stream sulfathiazole was omitted during the 7th week, to be resumed later in smaller doses. During the last 5 weeks the blood cultures remained sterile and the patient gradually improved. On discharge to convalesce at home she had no complaints other than a dull, aching pain in the back and some weakness. She remained at home in bed for 4 weeks and then re-entered the hospital in a critical condition. She was unresponsive, and no history could be obtained from her. However, it was learned that a week before entry she had begun to complain of pain in the back and high fever. Examination showed an injected pharynx. There were no abnormal findings in the chest. A soft systolic murmur

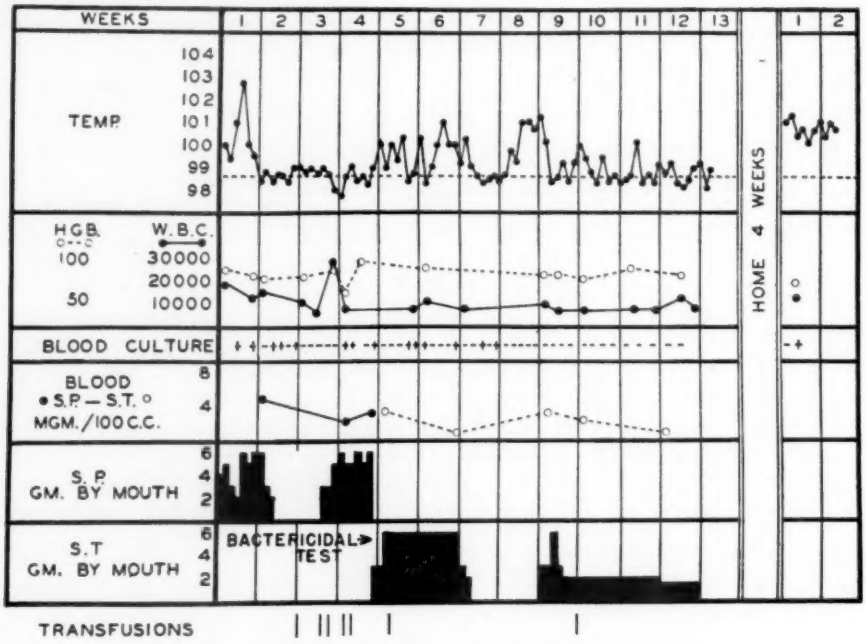

FIGURE 1. Staphylococcus aureus *Bacteremia with Death.*
S.T. = *sulfathiazole;* S.P. = *sulfapyridine.*

TABLE 1. *Bactericidal Effect of Defibrinated Blood on* Staphylococcus aureus *before and Two Hours following Oral Administration of 4 Gm. of Sulfathiazole.*

Blood		Factor	Dilution of Culture							
			10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}
Case 1*	Before S.T.	Hemolysis	++++	++++	0	0	0	0	0	0
		Colonies per cc.			700	550	55	76	80	0
	After S.T.	Hemolysis	++++	0	0	0	0	0	0	0
		Colonies per cc.		1,800	450	30	0	0	0	0
Case 2†	Before S.T.	Hemolysis	++++	++++	++++	++++	++++	0	0	0
		Colonies per cc.						Many	0	0
	After S.T.	Hemolysis	++++	++	0	0	0	0	0	0
		Colonies per cc.			1,400	24	0	0	0	0
Case 3‡	Before S.T.	Hemolysis	++++	++	0	0	0	0	0	0
		Colonies per cc.			Many	Many	20,000	6,400	8,000	0
	After S.T.	Hemolysis	++++	0	0	0	0	0	0	0
		Colonies per cc.		160,000	10,000	25,000	2,000	400	576	0

*Case 1. Concentration of sulfapyridine was 3.5 mg. per 100 cc. of blood before administration of sulfathiazole; the 10^{-6} dilution of the culture contained 4 organisms per cubic centimeter.

†Case 2. Concentration of sulfanilamide was 5.7 mg. per 100 cc. of blood before administration of sulfathiazole; the 10^{-5} dilution of the culture contained 3 organisms per cubic centimeter.

‡Case 3. Concentration of sulfapyridine was 10.4 mg. per 100 cc. of blood before administration of sulfathiazole; the 10^{-8} dilution of the culture contained 21 organisms per cubic centimeter.

was heard over the apex of the heart; the blood pressure was 140/70. The abdomen was soft, and no masses could be felt. There was bilateral ankle clonus and a doubtful Babinski sign on the right side.

Laboratory examinations showed a hemoglobin content of 60 per cent and a white-cell count of 14,500. The nonprotein nitrogen was 23 mg. per 100 cc. A lumbar puncture showed an initial pressure of 230 mm. of water, with normal dynamics. The fluid was xanthochromic, contained no cells and had an increased protein content. An x-ray film of the spine revealed a collapsed 11th dorsal vertebra. Over this vertebra marked tenderness was noted. The blood culture was again positive for *Staph. aureus*. The patient remained stuporous and expired on the 8th hospital day. Permission for a post-mortem examination could not be obtained.

Comment. This 62-year-old woman had signs of pulmonary infiltration, and the blood contained *Staph. aureus* on culture. No focus of infection other than the lesion in the lung could be found during the first admission. During the 1st month the patient was given sulfapyridine but the blood cultures remained positive. At the end of the 4th week in the hospital, sulfathiazole therapy was instituted, at which time a bactericidal test was done. Table 1 shows the results of this test. It can be seen from this table that the blood taken 2 hours after administration of 4 gm. of sulfathiazole showed an increase in the bactericidal power as compared to that of the blood taken before the test and containing sulfapyridine alone. For 3 days after the institution of sulfathiazole therapy the blood cultures were sterile, but later they again became positive. Because of the continued fever and some nausea, the drug was discontinued, to be readministered in smaller doses 10 days later. Gradually the temperature became lower, the blood cultures remained sterile, and the patient was discharged home. She remained in bed and during the week before re-entry had a recurrence of fever and complained of pain in the back. On admission she showed signs of spinal-cord compression. X-ray films revealed a collapse of the 11th dorsal vertebra. Blood culture was again positive for *Staph. aureus*. The patient expired 8 days later, the diagnosis being osteomyelitis of the 11th dorsal vertebra, extradural abscess and *Staph. aureus* bacteremia.

This patient was treated with blood transfusions and chemotherapy, and although an increase in the bactericidal power of the blood after the administration of sulfathiazole was demonstrated in a test against the patient's own organism, the blood did not remain sterile. Important in the fatal outcome of this case was the development of a metastatic lesion that was not amenable to surgical drainage.

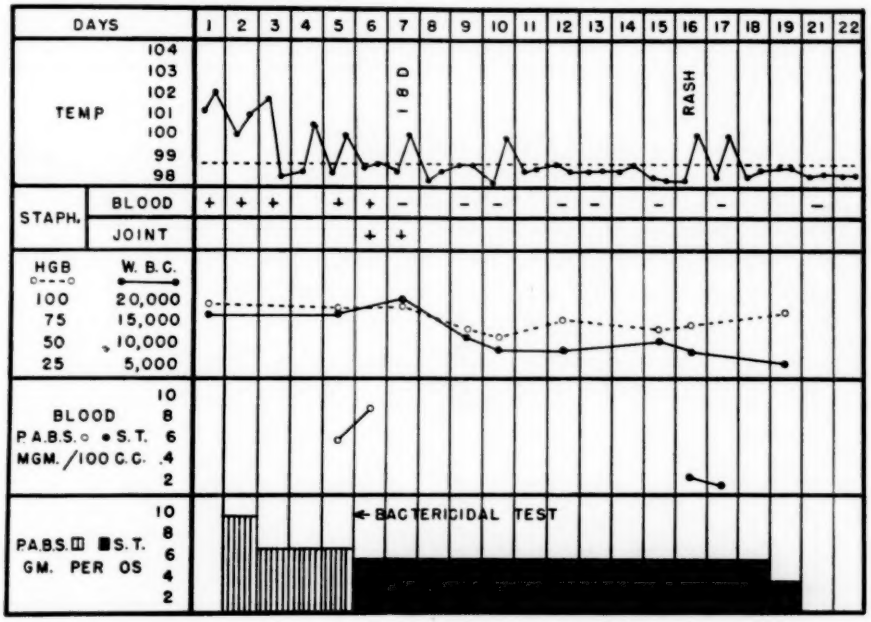

FIGURE 2. Staphylococcus aureus *Bacteremia with Recovery.*

P.A.B.S. = *sulfanilamide;* S.T. = *sulfathiazole.*

The positive blood culture on the sixth hospital day was taken before sulfathiazole was administered. The blood culture on the seventh day was taken before incision and drainage of the abscess.

CASE 2 (*Bacteremia with recovery*). A 27-year-old man entered the hospital because of pain in the right sternoclavicular joint. About a week before admission he had had an acute upper-respiratory infection; otherwise he had been in good health. Three days later he awoke early in the morning because of severe pain in the right sternoclavicular region. The joint became swollen and tender, and the pain was so severe that he remained in bed. The patient also had sensations of chilliness and sweating. Ten years previously he had had gonorrhea, but he denied any recent exposure to infection.

The temperature was 100.8°F., the pulse 110, and the respirations 24. The patient appeared well-nourished and had a warm, moist skin without eruptions. The tongue was dry and coated; the teeth were carious. The lung fields were clear. The heart was of normal size and the sounds were of good quality. The spleen and liver could not be palpated, and the prostate felt normal. There were

tenderness, hyperemia, swelling and induration over the right sternoclavicular joint. Movement of the joint caused severe pain.

Laboratory examination revealed that the urine was clear and normal. The white-cell count was 17,400, and the hemoglobin 94 per cent. Blood Hinton and gonococcal complement-fixation tests were negative.

Figure 2 shows the clinical course of the disease. Because of the involvement of the sternoclavicular joint and a history of a previous gonococcal infection, it was thought at first that gonococcal arthritis was the most likely diagnosis. Therefore, the patient was given sulfanilamide as indicated on the chart. On the 5th hospital day the blood culture taken on the day of entry was reported to be positive for *Staph. aureus*. The patient was then given 6 gm. of sulfathiazole daily. The blood showed an increased bactericidal effect, and the cultures became sterile. On the 7th hospital day the joint was incised and drained. Cultures of the pus showed *Staph. aureus*. On the 16th hospital day the patient developed a generalized maculopapular rash and sulfathiazole was discontinued. He was discharged well on the 22nd hospital day.

Comment. A 27-year-old man with a staphylococcal infection of the sternoclavicular joint and invasion of the blood stream was treated with sulfanilamide, sulfathiazole, and incision and drainage of the local infection. He made an uneventful recovery. During the treatment with sulfathiazole some anemia was noted, and on the 11th day after the institution of sulfathiazole the patient developed fever and a generalized skin rash. The fever and rash subsided immediately after withdrawal of the drug. A bactericidal test (Table 1) was done on the patient's blood while he was receiving sulfanilamide and again 2 hours after the administration of 4 gm. of sulfathiazole. The second specimen of blood showed a marked increase in the bactericidal effect against the strain of *Staph. aureus* that had been isolated from the blood stream of this patient.

Case 3 (*Bacteremia with death*). A 17-year-old boy entered the hospital complaining of pain in the region of the left hip joint. Eight days before admission he had fallen on the ice while skating, and although the hip was tender for a short time, he noticed no pain for 3 days. On the 4th day following the injury the left leg felt stiff, and that night he was awakened by a sharp, steady pain in both hips, which was severer on the left side. The pain was so intense that he had to remain in bed until the time of entry. The past history revealed that he had had several boils on his neck during the month or two before entry.

Physical examination showed a boy who appeared acutely ill. Both pupils reacted to light and accommodation, but the right pupil was slightly dilated. The heart rate was rapid, and there was a soft systolic murmur at the apex. Abdominal examination revealed nothing abnormal; the spleen could not be felt. There were pain and tenderness on pressure over the left sacroiliac joint, but neither redness nor swelling was noted.

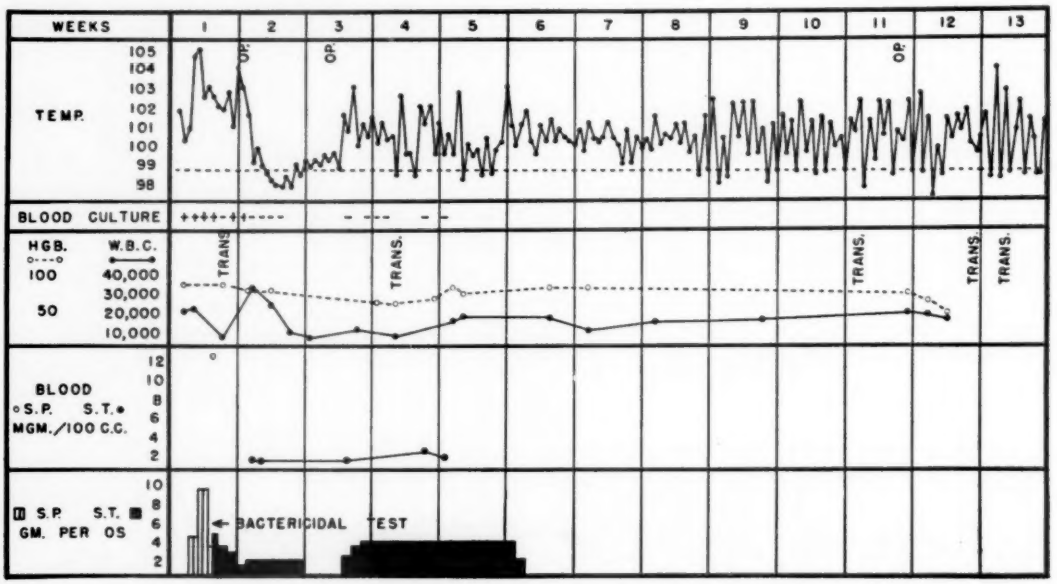

Figure 3. Staphylococcus aureus *Bacteremia with Death.*
S.P. = *sulfapyridine;* S.T. = *sulfathiazole.*

Laboratory examination showed a red-cell count of 4,200,000, with a hemoglobin of 85 per cent. The white-cell count was 20,500. The urine was normal. A blood Hinton test was negative. Lumbar puncture revealed a normal spinal fluid with no increase in cells. X-ray films of the hips and chest on admission showed nothing abnormal.

The clinical course of this patient's illness is shown in Figure 3. *Staph. aureus* was obtained on culture of the blood, and sulfapyridine was started immediately. On the 3rd hospital day there were 39 colonies of staphylococci per cubic centimeter of blood. On the 5th day sulfathiazole was administered, and on the following day the culture was sterile. The next two cultures, on the 7th and 8th days, were positive, but 1-cc. and 2-cc. pour plates showed no growth. Roentgenograms of the sacroiliac region were repeated, and they showed some destruction of the left sacroiliac joint. On the 8th hospital day the joint was drained, and cultures taken from the pus at the time of operation showed staphylococci. Following operation the temperature fell to normal and the blood cultures became sterile. In the 3rd week, following the removal

of the pack, the patient again began to show irregular fever. The cultures of the blood were sterile, but because of the fever sulfathiazole was again administered. Metastatic abscesses were searched for, but none were found. During the 11th week the left sacroiliac region was reexplored, and after chiseling through the lower part of the joint, a large pocket of pus was found. Because considerable bleeding was encountered, the joint was packed tightly. However, the patient continued to lose considerable blood from the wound, and during removal of the pack a few days later, severe bleeding occurred. Transfusions were given, but the bleeding did not stop. The patient died following a severe hemorrhage from the wound. Permission for a post-mortem examination was not obtained.

Comment. This 17-year-old boy had a staphylococcal infection of the left sacroiliac joint. Cultures of the coughing, and he began to perspire profusely and feel weak. These symptoms increased progressively until the time of admission. He had also noticed a foul odor around the upper portion of the cast.

Physical examination revealed a patient appearing critically ill. The respirations were 28. The skin was warm and moist. On percussion there was dullness over the right lower lung field posteriorly, and over this area rhonchi and coarse rales were heard. A few rales and diminished breath sounds were noted over the left base. The ribs were tender to pressure on both sides. The heart was not enlarged; no murmurs were heard; the rate was 140. The abdomen was normal. Around the upper portion of the cast a foul odor was noted, and pus could be seen oozing from the upper pinhole.

Laboratory examination revealed a red-cell count of 5,080,000. The white-cell count was 9800, with 86 per

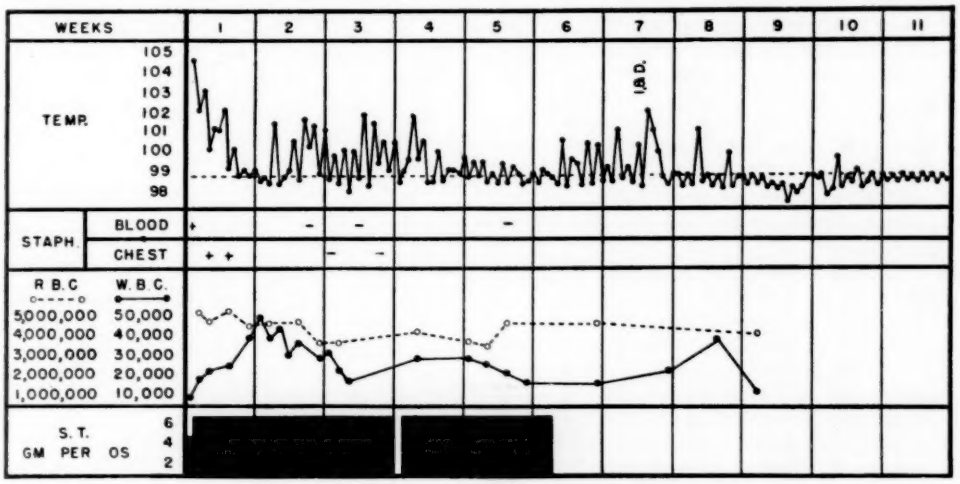

FIGURE 4. Staphylococcus aureus *Bacteremia with Recovery.*
S.T. = *sulfathiazole.*

blood were positive for *Staph. aureus.* Under sulfapyridine therapy the cultures remained positive. When sulfathiazole therapy was instituted, a bactericidal test was done, the results of which are shown in Table 1. The increase in bactericidal effect in this experiment following the administration of 4 gm. of sulfathiazole by mouth was not so marked as it was in Cases 1 and 2, but some increase was noted. The blood stream was not completely sterilized by sulfathiazole; however, the pour plates showed a decrease in the number of organisms per cubic centimeter of blood. Local drainage was followed by a fall in temperature to normal and by sterilization of the blood stream. After removal of the pack in the 3rd week of illness the temperature again became elevated but the blood cultures remained sterile. Sulfathiazole had no apparent effect on the fever at this time. In the 11th week of illness exploration revealed another large cavity filled with pus. The patient died shortly after this operation, as a result of severe hemorrhage from the wound.

CASE 4 (*Bacteremia with recovery*). A 40-year-old man entered the hospital with the complaint of pain in the chest and chills. A month previously he had been admitted because of a fractured right femur, for which he had a Roger–Anderson reduction. Two weeks later the pins were removed and the patient was discharged home to convalesce. About a week before the present entry he began to have pain in the chest, which was aggravated by cent polymorphonuclear neutrophils. The urine showed a + reaction for sugar, and the sediment contained a few red blood cells and white blood cells. A blood Hinton test was negative. The nonprotein nitrogen was 29 mg. per 100 cc.

The clinical course of this patient is shown in Figure 4. After a blood culture was taken the patient was started on sulfathiazole therapy. An x-ray film of the chest on admission showed infiltration at the left base. The patient was known to have diabetes, but it was well controlled on 5 to 15 units of insulin daily. On the 3rd day in the hospital he developed signs of fluid at the left base; a thoracentesis was done, the culture of fluid showing *Staph. aureus.* A second culture of the chest fluid on the 5th day yielded the same organism. On the 7th day the cast was removed and the patient placed in a Thomas splint. Under therapy with sulfathiazole the cultures of the blood and of the chest fluid became sterile, but the patient continued to have a low-grade fever and leukocytosis. Sulfathiazole was discontinued during the 6th week in the hospital, and shortly thereafter the temperature increased. X-ray films at that time showed changes consistent with osteomyelitis of the proximal fragment of the femur. In the 7th week more adequate drainage was established, and thereafter the temperature gradually returned to normal.

Comment. A 40-year-old man developed a staphylo-

coccal bacteremia and empyema following a fracture of the right femur. Sterilization of the blood stream and empyema followed sulfathiazole therapy. Later, after the establishment of adequate drainage of the focus of osteomyelitis, the temperature returned to normal, and he recovered.

Case 5 (*Bacteremia with death*). A 59-year-old man entered the hospital complaining of pain in the left leg. Seven weeks before admission he slipped and fell on the left knee, and several nights later it began to swell and became painful. However, he continued his work as a longshoreman. Three weeks before admission to the hospital the knee became stiff and the pain grew much worse. In addition, for 1 week prior to admission he had noted some aching in the right shoulder. No further history could be obtained.

On admission the temperature was 99°F., the pulse 100, and the respirations 28. The skin was dry, pale and warm. The lower teeth were carious, and the pharynx was injected. The trachea was in the midline. Dullness, harsh breath sounds and rhonchi were present over the apices posteriorly on both sides. The heart was not enlarged; the rhythm was regular, and no murmurs were heard. The spleen was not enlarged, and no masses were palpated in the abdomen. The left knee was swollen, and there was redness over the lateral portion of the knee and the upper tibia. Fluctuation was present, and motion of the joint caused pain.

Laboratory examination showed a urine with a specific gravity of 1.022, a trace of albumin and a positive test for acetone. The sediment showed a moderate number of white blood cells. The red-cell count was 3,300,000, the white-cell count 13,600, and the hemoglobin 72 per cent. Sputum examination revealed no acid-fast organisms. Two stool examinations gave a positive guaiac test for blood.

A short time after admission the patient coughed up a considerable amount of blood; it was impossible to tell whether it came from the stomach or the lungs. The hemoglobin fell to 40 per cent, and the patient was given a transfusion. Cultures of the blood and of the fluid aspirated from the knee joint showed *Staph. aureus*. The knee was incised and drained on the 3rd hospital day. X-ray films of the knee showed erosion of the lateral aspect of the tibia. On admission the patient was given sulfapyridine, but on the 4th hospital day this was changed to sulfathiazole. The temperature was subnormal until it rose to 101°F. terminally. He died on the 7th day in the hospital.

Comment. In summary, this 59-year-old man entered the hospital with pyogenic arthritis of the left knee, osteomyelitis of the tibia, signs of consolidation in the lung and a blood-stream infection due to *Staph. aureus*. Soon after admission he had a severe hemorrhage from the mouth. In spite of transfusions, sulfapyridine therapy for 4 days and sulfathiazole for 3 days, he expired on the 7th hospital day.

Case 6 (*Bacteremia with death*). A 47-year-old woman entered the hospital complaining of pain in the right knee joint. Four days before admission she developed a shaking chill and noticed pain in the right knee joint, which was aggravated by motion. Soon after the chill there was slight swelling in the knee joint.

There was no history of previous staphylococcal infection. For several days she had noticed slight urinary frequency, and nocturia with dysuria. A mild cough had been present, which was productive only of whitish sputum.

Physical examination revealed a very obese woman with a temperature of 105°F., a pulse of 128 and respirations of 40. The skin was warm and moist; no eruptions were noted. The tongue was coated. The pharynx was not injected. Chest expansion was equal on both sides. The trachea was in the midline. Dullness to percussion was present over the left base, without changes in breath sounds. A few scattered rales were heard at the right base. No tenderness or masses were noted in the abdomen. The right knee was swollen slightly, but there was no local redness or signs of fluctuation. Marked pain was caused by motion of the knee.

Laboratory examination revealed that the urine was normal except for a trace of albumin and numerous white cells in the sediment. The hemoglobin was 87 per cent, and the white-cell count 10,200; blood Hinton and gonococcal complement-fixation tests were negative. The nonprotein nitrogen was 30 mg. per 100 cc. An electrocardiogram was reported as normal. Sputum examination showed no pneumococci.

The patient was treated symptomatically. On the 3rd day the temperature was still elevated, the knee was markedly swollen and somewhat red, and questionable fluctuation was present. A chest film on the 3rd day showed patchy infiltration at both bases. An x-ray film of the knee joint revealed narrowing of the joint space and swelling of the soft tissues. No bony changes were noted. On the 5th day the cultures of the blood were reported as containing *Staph. aureus*. The patient was started on sulfathiazole, 6 gm. daily, at this time. Before the knee joint could be drained she died.

Comment. This 47-year-old woman was admitted to the hospital with symptoms of pyogenic arthritis of the right knee. *Staph. aureus* had invaded the blood stream, and there was x-ray evidence of metastatic lesions in the lung. Sulfathiazole therapy was instituted, but the patient expired 24 hours later.

Case 7 (*Bacteremia with recovery*). A 13-year-old boy entered the hospital because of severe pain in the right forearm. Three days before admission a streetcar door closed on his right arm. The next day he began to complain of pain in this area. The mother noticed at this time that the arm was swollen and tender. There was no previous history of staphylococcal infections.

Physical examination showed redness, swelling and local tenderness over the lower third of the right radius. The lymph nodes in the right axilla were slightly enlarged. The lungs were resonant to percussion, and no rales were heard. Auscultation of the heart revealed nothing abnormal. The liver and spleen were not palpable.

Laboratory examination showed a normal urine. The white-cell count was 13,600, and the red-cell count 4,120,000, with a hemoglobin concentration of 85 per cent. Roentgenograms revealed destruction of the distal end of the right radius, with marked soft-tissue swelling in this area.

Soon after admission the boy had a chill, the temperature reaching 103°F. Blood withdrawn during the chill was cultured and showed *Staph. aureus*. The day after entry the area of osteomyelitis was drained. Cultures of the pus showed *Staph. aureus*. The wound was packed with vaseline gauze and a posterior splint applied. Sulfathiazole was administered in a dosage of 0.75 gm. every 4 hours. The concentration of the drug in the blood varied from 1.8 and 5.1 mg. per 100 cc.

Following operation the temperature remained slightly elevated and two blood cultures showed *Staph. aureus*. Because of the low-grade fever and positive blood cultures the vaseline pack was removed on the 13th postoperative day. The temperature immediately returned to normal

and the blood cultures became sterile. Ten days after the institution of chemotherapy the conjunctivas became injected. Several days later a lesion simulating erythema nodosum appeared over the lower extremities. Sulfathiazole was discontinued, and the skin lesions rapidly disappeared.

Comment. A 13-year-old boy had osteomyelitis of the radius and staphylococcal bacteremia. The clinical course of the illness was especially interesting. Drainage of the localized abscess failed to sterilize the blood stream, and in addition, the temperature remained elevated. It was not until the vaseline pack had been removed and adequate drainage established that the patient recovered.

Bactericidal Studies Following the Administration of Sulfathiazole by Mouth

Methods

The bactericidal tests here reported were carried out following a technic described in a previous publication.[9] The organisms used were isolated from the blood stream of Cases 1, 2 and 3 and from a case of osteomyelitis of the rib. All strains produced yellow pigment on blood agar and also gave a positive coagulase reaction. The organisms were stored on blood-agar slants, and sixteen-hour peptone-broth cultures were used in all experiments.

Each patient (Cases 1, 2, 3) and all the normal subjects used in this study were given 4 gm. of sulfathiazole by mouth. Under sterile precautions, venous blood was withdrawn before the administration of sulfathiazole and again two hours after the administration of the drug. Each blood sample was defibrinated, and 0.5-cc. amounts were placed in eight pyrex test tubes. To each of these tubes 0.1 cc. of a saline dilution, ranging from 10^{-1} through 10^{-8} of the sixteen-hour peptone-broth culture, was added. The tubes were sealed in a gas-oxygen flame and rotated in the incubator at 37°C. for forty-eight hours. The tubes were then examined for hemolysis; those showing no hemolysis were plated out and the colonies counted. The number of organisms contained in the original inoculum was calculated from the number of organisms contained in 0.25 cc. of the fluid in the eighth tube. The concentration of the drug in the blood was determined at the time of withdrawal of the specimens.

Results

Figure 5 shows in a graphic form the results observed following the administration of 4 gm.

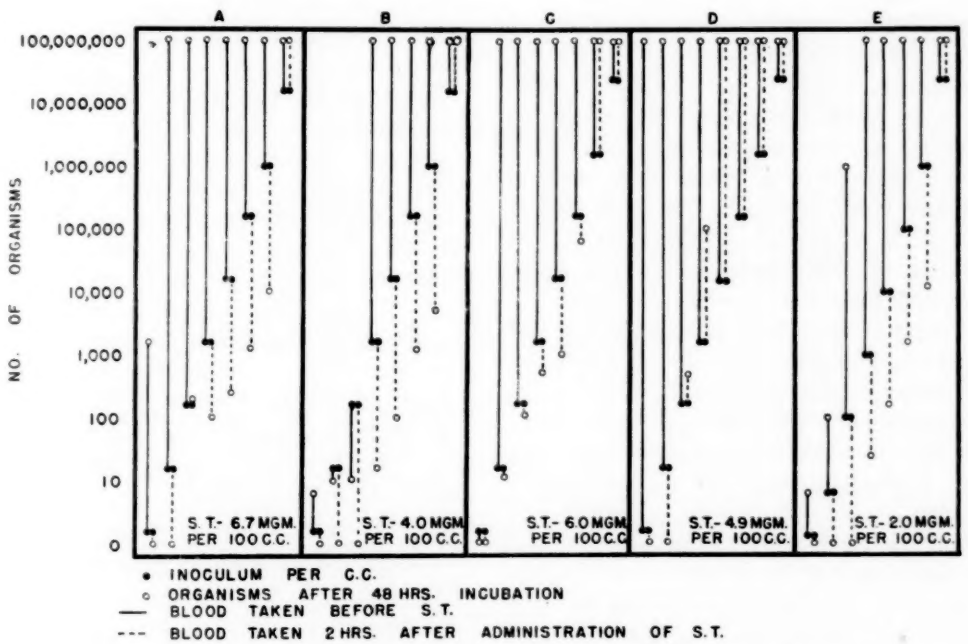

Figure 5. *Bactericidal Effect on* Staphylococcus aureus *in Normal Defibrinated Blood following the Oral Administration of 4 Gm. of Sulfathiazole.*
S.T. = *sulfathiazole.*

Experiment D is an exception to this statement. Here, when the original inoculum was over 20 organisms per cubic centimeter, no bactericidal effect was observed. However, bacteriostasis was demonstrated. This cannot be explained by a low level of sulfathiazole in the

of sulfathiazole by mouth to 5 normal persons. In general, if the original inoculum was 1,000,000 organisms per cubic centimeter or less, a bactericidal effect was demonstrable after forty-eight hours' incubation.

blood, since the concentration here was more than twice the concentration in Experiment E. Rather, it appears that blood capable of producing some bacteriostasis normally will exhibit even more marked bacteriostasis and bactericidal action following the administration of sulfathiazole by mouth.

In the experiments performed with the bloods of patients with *Staph. aureus* bacteremia against their own organisms, each sample contained either sulfanilamide (Case 2) or sulfapyridine (Cases 1 and 3) at the time these tests were carried out. The concentration of the various drugs in the blood before the administration of sulfathiazole is recorded in Table 1. In all three cases there was an increase in the bactericidal effect following the administration of sulfathiazole; this was most marked in the patient that was already receiving sulfanilamide (Case 2).

Comment

Seven cases of *Staph. aureus* bacteremia were treated with sulfathiazole; 3 recovered (Cases 2, 4 and 7). The number of cases treated is too small to judge the efficacy of sulfathiazole therapy. However, it is worth mentioning a few factors that influenced the course of these cases. Four of the patients (Cases 1, 4, 5 and 6) were forty years of age or older, and one of them recovered (Case 4). Of 40 patients over forty years of age, Skinner and Keefer[4] observed that only 1 recovered. Mendell[3] reports 1 recovery in 9 patients over forty years of age. Perhaps more important than the age of the patients treated is the accessibility of metastatic abscesses to surgical drainage. In the 3 patients who recovered (Cases 2, 4 and 7) the abscess was drained. In Case 4, there was, in addition to the abscess in the right thigh, an empyema that became sterile during sulfathiazole therapy. In the series of 22 patients who recovered that was studied by Skinner and Keefer,[4] 21 had localized lesions that were incised and drained. It seems justifiable, then, to state that surgical drainage of the localized staphylococcal abscesses is essential to recovery in most cases.

With the exception of sterilization of the empyema cavity in Case 4, we have not observed an abscess that became sterile under treatment with sulfathiazole. What place, then, has the drug in the treatment of these infections? We have demonstrated that sulfathiazole when given by mouth to normal persons and to patients with bacteremia increases the bactericidal and bacteriostatic action of the blood against pathogenic staphylococci. In our experience sulfathiazole either sterilized the blood stream or lowered the number of organisms in the circulating blood. This action may be valuable in the prevention of metastatic abscesses during the period of blood-stream invasion. It has been pointed out that 82 per cent of all cases with bacteremia develop secondary lesions, and it is the development of these metastatic abscesses which cannot be drained that determines the fatal outcome in the majority of cases.

To summarize, patients suspected of having a bacteremia due to *Staph. aureus* should have a blood culture done as soon as possible, following which sulfathiazole should be administered immediately. Daily blood cultures should be taken, and determinations of the concentration of sulfathiazole in the blood should be made. It is desirable to maintain a level of sulfathiazole in the blood stream of between 3 and 5 mg. per 100 cc.[9] If the patient is anemic, blood transfusions should be given until the blood count is normal. The diagnosis and immediate drainage of all localized abscesses are of utmost importance. A sustained fever or blood cultures that continue to be positive are usually signs of further abscess formation, and a thorough search should be made for such lesions.

Treatment with sulfathiazole should not be undertaken without close observation for toxic manifestations. For this reason daily blood counts and urine analyses should be made. In the cases reported here no serious toxic manifestations were observed. Two patients (Cases 1 and 3) complained of nausea and occasionally vomited. One patient (Case 2) developed a mild anemia and on the eleventh day of treatment a generalized rash and fever were noted, which disappeared promptly following withdrawal of the drug. Case 7 showed injection of the conjunctivas and a lesion simulating erythema nodosum. No marked anemia or hematuria due to sulfathiazole was noted in these cases.

Conclusions

Seven cases of *Staphylococcus aureus* bacteremia were treated with sulfathiazole, and 3 recovered.

Following the administration of sulfathiazole in 3 cases, an increase in the bactericidal action of the blood against the invading organisms was demonstrated.

In normal persons the oral administration of sulfathiazole increases the bactericidal action of the blood against *Staph. aureus.*

Sulfathiazole usually sterilizes or decreases the number of organisms in the circulating blood, and therefore should be valuable in preventing the formation of metastatic abscesses.

The importance of blood transfusions and surgical drainage of localized abscesses is stressed.

78 East Concord Street

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TULAREMIA

Report of a Case Contracted on Cape Cod*

ROBERT E. MOSS, M.D.,† AND LLOYD R. EVANS, M.D.‡

BOSTON

TULAREMIA, specifically recognized, has been very rare in Massachusetts and the other New England states. In 1939, Badger[1] reported the second case diagnosed in this commonwealth — the fifth recorded in New England. Yet Cape Cod is infested with common wood ticks (*Dermacentor variabilis*), and in 1937 cottontail and jack rabbits imported from the West were released in this area both by state game conservation officers and by local sporting clubs. Badger's case, the first ever reported on the Cape, was contracted at West Falmouth in 1937.

Since that time, 2 additional cases of tularemia have been reported to the Massachusetts Department of Public Health,[2] 1 in 1938 and 1 in 1939. The latter chanced to come under our care as a routine hospital admission. Because of the conditions that favor the propagation of tularemia in the Cape Cod area, and the likelihood of disregarding the possibility of the disease in a specific case unless one's suspicion is aroused, we believed that this case should be reported.

CASE REPORT

C. G. N. (Medical No. 55,607), a 52-year-old widow, was admitted to the Medical Service of the Peter Bent Brigham Hospital on August 7, 1939, complaining of diarrhea and constipation, accompanied by fever, during the previous week.

The past history contributed nothing to an understanding of the illness, except that the patient had spent the week prior to onset at a hotel in Falmouth on Cape Cod. She stated that the food had been bad and had made the help sick earlier in the summer.

She had been well, except for mild menopausal symptoms, until the evening of July 30, when she felt a "hot flash." This was accompanied by nausea, followed by vomiting. Thereafter she felt fairly well, although somewhat feverish. Later in the evening she again vomited material containing nothing resembling blood or coffee-grounds. She found her temperature to be 104°F., and called her physician, who confirmed the temperature reading. That night she slept poorly because of a feeling of warmth and an intense headache. Also, she "ached all over," as if she were "getting the grippe."

The next day she remained in bed, following a liquid diet prescribed by her physician. She had one watery bowel movement, the temperature fell to 103°F., and she felt "wishy-washy." Thereafter, she remained in bed up to the time of admission.

On August 1, she found a small flat bug on her nightgown, and noted a small, sore spot, resembling a mosquito bite, on the posterior surface of the left thigh. Again, she had one watery bowel movement. Then, a dry, hacking cough developed, which persisted, though diminishing in frequency, until admission. A "cold sore" appeared in the mouth at this time. The next day the headache was almost negligible, and the temperature was normal.

On August 3, she had no bowel movement. In the morning, she had "chills," and the temperature went to 101°F., where it remained for the next 3 days, with an afternoon rise to 102. On August 6, she felt well enough to take solid food, which was well tolerated. The next day, she was given a productive enema. Because the temperature was still 102°F., and because he was leaving the city, her physician referred her to the hospital for further study.

The patient had applied poultices of hot boric acid solution to the sore spot on the left thigh. The area had increased in size, however, and without forming a pustule had formed a central scab. Other treatment had

*From the Medical Clinic, Peter Bent Brigham Hospital.

†Assistant resident physician, Massachusetts Memorial Hospitals; formerly, medical house officer, Peter Bent Brigham Hospital.

‡Voluntary graduate assistant, Peter Bent Brigham Hospital.

consisted of powders for diarrhea and vomiting, and aspirin while the headache persisted.

Physical examination showed a well-nourished and well-developed woman. She seemed very warm, tolerating only the lightest covering, and was moderately restless. No sign of the previous cold sore persisted about the mouth. The heart was slightly enlarged, but otherwise appeared normal. The blood pressure was 118/80. The lungs were normally resonant and without abnormal sounds. The abdomen was not distended or tender; no masses or organs could be felt. On the lower third of the posterior aspect of the left thigh was a red wheal 4 cm. in diameter, in the center of which was a black scab 1 cm. in width. A slightly enlarged, firm, nontender node was felt in the femoral triangle on the left. Examination was otherwise not noteworthy.

On admission the urine showed a slight trace of albumin, with a negative sediment. On the 3rd day there was a very slight trace of albumin with an occasional white blood cell in the sediment. Thereafter, examination of the urine was negative, except for a rare red blood cell in one specimen, and 10 or 12 white blood cells per high-power field in another.

The hemoglobin ranged from 95 to 105 per cent (Sahli). The red-cell count varied from 3,000,000 to 4,400,000. The white-cell count was 11,750 on admission, rose to 14,600 on the third day, fell to 8850 on the twelfth day, and was 10,950 when last taken a week before discharge. The differential count showed 72 per cent polymorphonuclears, 13 per cent large lymphocytes and 15 per cent small lymphocytes. Blood Wassermann and Hinton tests were negative. The corrected sedimentation rate on August 19 was 19 mm. in 10 minutes. Blood cultures were done daily for 12 days and were all negative. A Widal test on August 10 was negative in dilutions from 1:1 to 1:100. Agglutination tests against paratyphoid A and B bacilli were questionably positive in a 1:1 dilution, but negative in dilutions of 1:25 and 1:50.

The Bacteriological Laboratory of the Massachusetts Department of Public Health reported that blood taken on the 2nd day showed negative agglutination tests against typhoid and paratyphoid A and B bacilli, *Brucella abortus*, dysentery organisms and *Proteus X19*. On August 14 the same laboratory reported a positive Weil–Felix reaction in a dilution of 1:25. Beginning on the 2nd day, four blood specimens were sent to the National Institute of Health for agglutination tests. The results are shown in Table 1.

TABLE 1. *Dilutions Giving Positive Agglutination Tests, as Reported by the National Institute of Health.*

DATE SPECIMEN TAKEN	*Past. tularensis*	*Br. abortus*	*E. typhi*	*Proteus X19*	*Proteus OX2*
8-8-39	0	0	0	1:80	0
8-14-39	1:320	0	0	1:40	1:10
8-22-39	1:1280	1:80	1:10	1:40	1:20
8-30-39	1:1280	1:20	1:10	1:20	

Repeated stool cultures were negative, except for *Escherichia coli*. A brucellergin skin test was negative at 10 minutes, showed a +++ reaction at 24 hours and a + reaction at 48 hours. On August 31, a *Pasteurella tularensis* skin test, performed with material supplied by Dr. Lee Foshay, gave a 0.7-cm. wheal with a 5.0-cm. area of erythema at 48 hours. Blood injected into a male guinea pig on August 14 showed no evidence of Rocky Mountain spotted fever.

An x-ray film of the chest, taken with a portable machine, showed the lungs to be clear on August 9.

The temperature on admission was 102.4°F., with a pulse rate of 84 and respirations of 34. The temperature fell by lysis, reaching normal on the 15th day, but rose above 99°F. nearly every afternoon until discharge. The pulse tended to remain between 80 and 90, although the respirations usually ranged between 20 and 25. The bowels moved once or twice daily. At no time did the patient appear seriously ill.

Seven months after discharge the patient reported that she felt well. Her physician stated that the lymph node in the left groin had finally suppurated, requiring incision and drainage 3 weeks after discharge. Then the slight fever that had recurred while the lymph node was suppurating subsided permanently, despite the fact that the wound drained for about 3 months.

On admission, the most likely diagnosis was tularemia. This rare infection was suspected because of the excellent report by Badger,[1] in which he pointed out the presence of an almost ideal "tularemia set-up" on Cape Cod. The diagnoses that had to be ruled out were typhoid fever, Rocky Mountain spotted fever and tick-bite fever. Disparity between temperature and pulse rate and a story of having eaten bad food that allegedly had sickened others suggested typhoid fever, but it was rather easily ruled out by the repeatedly negative blood and stool cultures and Widal tests. Although we had no opportunity to see the insect found by the patient, we had to assume that it probably was a tick, and hence that she might have a tick-transmitted infection other than tularemia. The diagnosis was settled by the laboratory tests. The first reports of the agglutination tests from both the state and federal laboratories pointed toward spotted fever, despite the total lack of clinical evidence for this diagnosis. Table 1 shows that the agglutinin titer for *Proteus X19* fell, whereas that for *Past. tularensis* rose strikingly. The guinea-pig test for Rocky Mountain spotted fever was negative. According to Badger,[1] Foshay reports frequent cross-agglutination of *Proteus X19* in animals infected with tularemia, but rarely in man. Badger's case did not show a positive Weil-Felix reaction. Cross-agglutination of *Br. abortus* by tularemic serums has frequently been noted.[3] Further proof of the correct diagnosis was obtained by means of the skin test with Dr. Foshay's preparation of *Past. tularensis*. This test was strongly positive according to his standards.[4]

Treatment of tularemia can be undertaken with a specific serum,[4] or with sulfanilamide.[5] Neither was considered vitally necessary, however, in this case, since the patient at no time appeared seriously ill. She was therefore given only bedrest and general care, and recovered, following the suppuration of the left inguinal node, which was in-

cised three weeks after her discharge and which drained for three months. Whether serum therapy might have prevented this complication cannot be stated.

Summary

A case of ulceroglandular tularemia, contracted on Cape Cod, is reported. The potentialities of this tick-infested area as a source of future cases of tularemia are emphasized.

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PNEUMOCOCCAL CROSS-INFECTIONS IN THE HOME AND HOSPITAL*

Henry A. Holle, M.D.,† and Jesse G. M. Bullowa, M.D.‡

New York City

THE refinement of the immunologic classification of the pneumococci by Cooper and her co-workers has facilitated the epidemiological study of the transmission of the pneumonias. The pneumococci present no distinguishing microscopic appearance. Formerly it was widely believed that the pneumococci often found in the nose and throat of healthy persons had no connection with the transmission of the disease, and that they were transformed into pathogenic forces by some unknown conditions or factors. Accordingly, many physicians and hospital administrators thought that precautions against the spread of the pneumonias were unnecessary. So long as it was impossible to distinguish different phases of a pneumonia as due to separate infections, many cases of cross-infection among pneumonias were not recognized, and recrudescence of fever was usually regarded as an exacerbation of the original disease.

Familial infections have been followed and reported by a number of observers,[1-6] but the recording of additional cases is valuable because of current widespread beliefs and practices that ignore the opportunity for prophylaxis. The first patient stricken in a family is rarely segregated, and when sent to hospitals patients are rarely individualized by an aseptic nursing and staff technic such as that used in the best hospitals for patients with infectious disease.

Cross-infections occur both in the home and in the hospital ward. Pneumococcal pneumonia is an acute communicable disease. The following hitherto unreported cases are given as evidence of contagious infection. Five examples of cross-infection among families in the home, with the cases later admitted to the Harlem Hospital, and four cases developing on the wards of the hospital are presented.

*From the Littauer Pneumonia Research Fund, and the Medical and Pediatric services, Harlem Hospital, New York City. These studies received financial support from the Metropolitan Life Insurance Company and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch, Jr., Miss Belle N. Baruch and Mrs. H. Robert Samstag.

†Passed assistant surgeon, United States Public Health Service.

‡Clinical professor of medicine, New York University College of Medicine; visiting physician, Harlem Hospital.

Family Infections

S Family

Case 1. A. S., 7-year-old boy.

12/19/38. Onset with cough and fever.
12/21/38. Admitted to hospital; lobar pneumonia in right lower lobe, confirmed by x-ray examination.
12/22/38. Type 2 pneumococcus recovered from sputum; also alpha hemolytic streptococcus.
12/28/38. Discharged.

Case 2. C. S., 5-year-old girl. Sister of A. S.

12/24/38. Onset with cough, fever, chest pain.
12/28/38. Admitted to hospital; clinical and x-ray findings of consolidation of left lower lobe; Type 2 pneumococcus recovered from sputum.

In the S family, Type 2 pneumococcus pneumonia occurred in a younger sister within 3 days after the first patient was hospitalized, and within 5 days of the onset of the first patient.

C Family

Case 1. S. C., 9-year-old boy.

12/26/38. Onset with cough and fever.
12/29/38. Admitted to hospital; lobar pneumonia in right lower lobe.
12/30/38. Type 1 pneumococcus recovered from sputum.

Case 2. A. C., 38-year-old woman. Mother of S. C.

12/27/38. Onset with chills, fever, cough.
1/3/39. Admitted to hospital; signs of pneumonia in right lower lobe, confirmed by x-ray films; Type 1 pneumococcus recovered from sputum and blood.

Case 3. L. C., 18-year-old girl. Sister of S. C.

12/29/38. Onset with pain in left chest, cough, chills, fever.
1/3/39. Admitted to hospital. Signs of consolidation in left lower lobe, confirmed by x-ray examination; Type 1 pneumococcus recovered from sputum and blood.

Case 4. C. C., 49-year-old man. Father of S. C.

12/30/38. Onset with chill, pain in left chest, fever, cough.
1/3/39. Admitted to hospital; signs of consolidation in left lower lobe, confirmed by x-ray studies.
1/4/39. Type 1 pneumococcus recovered from sputum.

Case 5. D. C., 6-year-old girl. Sister of S. C.

Date of onset unknown.
1/4/39. Admitted to hospital; diagnosis, lobar pneumonia.
1/?/39. Type 1 pneumococcus recovered from sputum.

Case 6. R. S., 3-year-old girl. Sister of S. C.

Date of onset unknown.
1/6/39. Admitted to hospital; diagnosis, lobar pneumonia; Type 1 pneumococcus and beta hemolytic streptococcus found in sputum.

The 7 members of the C family lived together in a small five-room apartment. S. C. (Case 1) slept with H. C., the only member of the family to escape infection with Type 1 pneumococcus. S. C. developed a cough with fever on December 26, 1938, and because he appeared so sick he slept with his mother, A. C. (Case 2), from December 26 to 29, at which time he was admitted to the hospital. A. C. developed chills, fever and a cough on December 27 and went to bed, but got up at intervals to administer to her sick family. She was finally admitted on January 3, 1939, with a bacteremia.

S. C. was taken to the hospital on December 29, 1938, by L. C. (Case 3), an older sister. It was necessary for L. C. to wait for some time before S. C. was admitted. As a result she missed her dinner and got very cold. While waiting she held S. C.'s head in her lap. That night she developed chills and slept with her mother, A. C., who was already ill. She was admitted with A. C. on January 3.

C. C. (Case 4) nursed his wife, A. C., and daughter, L. C., after working-hours until he became ill on December 30, 1938. He was admitted on January 3, 1939.

D. C. (Case 5) and R. S. (Case 6) slept in the same bed. The exact dates of the onset of their pneumonias are not known, but judging from the fact that the mother did not know of their illness until later, it is assumed that the onset occurred after the latter had left for the hospital on January 3. D. C. was admitted on January 4, and R. S. on January 6.

SU FAMILY

Case 1. E. S., 36-year-old man.

10/31/38. Onset with pain in right chest, cough, expectoration.
11/3/38. Admitted to hospital; signs of pneumonia in right lower lobe.
11/4/38. Type 5 pneumococcus recovered from sputum.

Case 2. E. S., Jr., 11-year-old boy. Son of E. S.

11/1/38. Onset with upper-abdominal pain.
11/5/38. Admitted to hospital; dullness in left lower lobe.
11/6/38. Type 5 pneumococcus recovered from pharyngeal aspirate; x-ray examination showed consolidation at left base.

Family Su is an instance of Type 5 pneumococcus pneumonia in a father followed 1 day later by a similar infection in the son.

P FAMILY

Case 1. R. P., 3-year-old boy.

12/25/38. Onset with cough and fever.
12/27/38. Admitted to hospital; signs of consolidation in left lower lobe, confirmed by x-ray film.
12/28/38. Type 5 pneumococcus recovered from sputum.
12/30/38. Types 5 and 14 pneumococci recovered from laryngeal evacuate.

Case 2. R. P., 3-year-old boy. Twin brother of R. P.

12/27/38. Admitted to hospital with upper-respiratory infection.
12/28/38. Temperature rose above 104°F.
12/29/38. Physical signs of pneumonia; no definite consolidation.
12/30/38. Type 5 pneumococcus recovered from pharyngeal aspirate.

The P family presents an interesting history of twin brothers. R. P. (Case 1) became ill on December 25, 1938, with cough and fever. He was admitted on December 27 with a diagnosis of pneumonia, Type 5 pneumococcus. R. P. (Case 2) was admitted at the same time with an upper-respiratory infection and developed a pneumonia due to Type 5 pneumococcus on the following day.

W FAMILY

Case 1. J. W., 9-year-old girl.

12/15/38. Onset with persistent cough.
12/20/38. Admitted to hospital; crepitant rales in right and left lower lobes; x-ray findings, scattered patches of consolidation in mid-portion of right lung; Type 1 pneumococcus recovered from sputum.

Case 2. C. W., 30-year-old woman. Mother of J. W.

12/25/38. Visited daughter in hospital.
12/26/38. Onset with chills, fever, pain in right chest, cough.
12/29/38. Admitted to hospital; clinical and x-ray findings consistent with pneumonia in right lower lobe.
12/30/38. Type 1 pneumococcus recovered from sputum.
12/31/38. Type 1 pneumococcus found in blood; patient later developed arthritis of left sternoclavicular joint, from which Type 1 pneumococcus was recovered.

C. W. (Case 2) slept with J. W. (Case 1) until the latter was admitted to the hospital.

Although the evidence that each of the infections described above was transferred from person to person within the several families is not incontrovertible, the occurrence of infections with identical pneumococcal types can hardly be explained as coincidence. The fact that these cases were observed during only two months suggests that simultaneous or almost simultaneous infections with identical pneumococcal types within families, such as the C family, are not uncommon. There is reason to believe that if each patient admitted were carefully questioned regarding other illnesses in the family, many additional cases of cross-infection would be discovered. Pneumonia prevention in the home seems to deserve more emphasis than has been placed on it in the past, and early isolation is probably an important factor. In addition, rapid active or passive immunization against specific types of the pneumococcus, with improved antigens or antiserums, and possibly chemoprophylaxis, offer themselves for study.

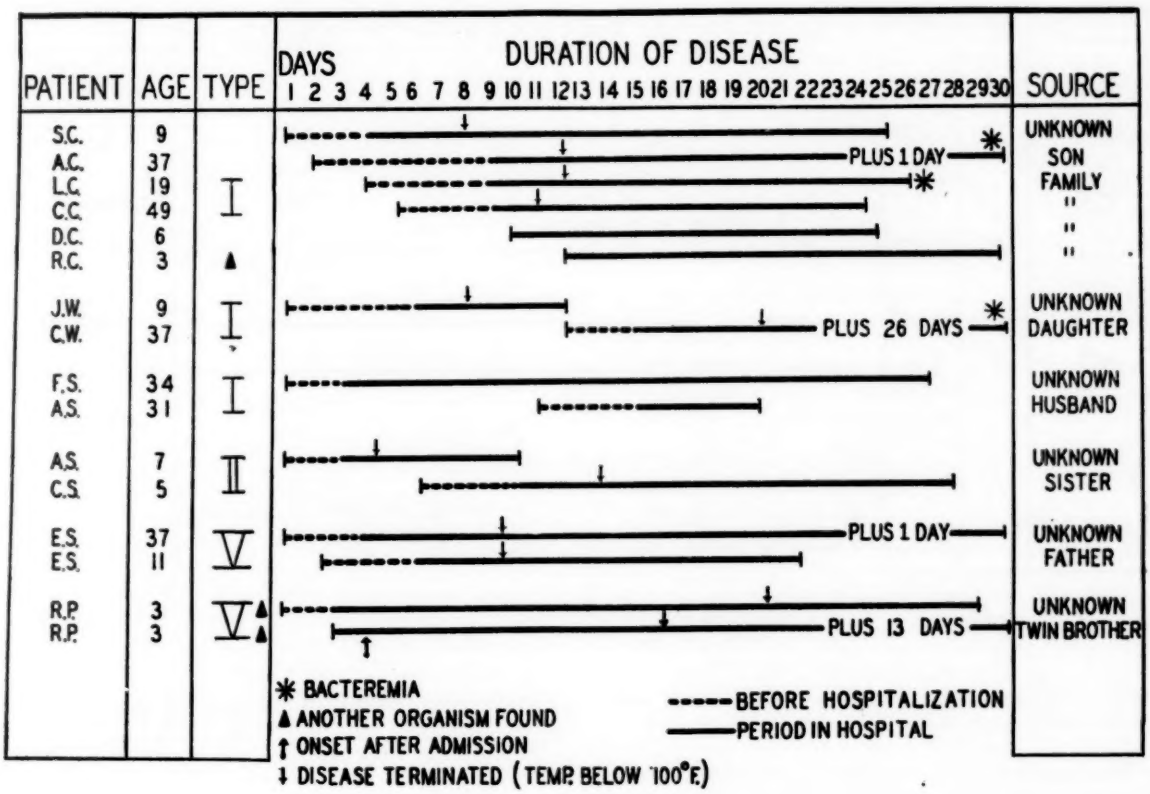

FIGURE 1. *Family Infections.*

HOSPITAL-WARD INFECTIONS

CASE 1. B. C., a 34-year-old woman, was admitted to the hospital on January 3, 1939, on the 2nd day of a pneumonia in the left lower lobe due to Type 7 pneumococcus. She was visited on January 9 by A. T., a 30-year-old woman, who was ambulant in the ward recuperating from pneumonia in the left lower lobe due to Type 5 pneumococcus, for which she had received therapeutic serum on January 4. A. T., who had been afebrile for 4 days, was seen at the patient's bedside and was immediately ordered back to bed. However, 2 days later the patient was seized with a severe pain in the right chest and had an elevation of temperature. Type 7 pneumococci were recovered from the sputum on the same day, and x-ray examination revealed an area of consolidation in the base of the right lung, which became more extensive on January 13.

CASE 2. G. S., a 46-year-old man, was admitted on July 2, 1937, and was found to have pneumonia of the left lower lobe due to Type 2 pneumococcus. From July 6 to 17 he occupied a bed adjacent to C. S., who had pneumonia of the left lower lobe due to Type 4 pneumococcus. On July 20 the patient complained of pain in the right chest and began a new febrile course. The next day Type 4 pneumococcus was found in the sputum, and x-ray examination of the chest revealed consolidation in the right lower lobe.

CASE 3. Dr. H., an intern at the hospital, was admitted on October 11, 1938, with pneumonia of the right upper lobe. Type 20 and Wilder-type pneumococci were recovered from the sputum, and he received appropriate treatment. During his illness a special nurse was assigned but on October 16 the nurse caring for C. T., who was in an adjacent ward recovering from a Type 2 pneumonia of the right lower lobe, was assigned to the patient, while still continuing to care for C. T. The next day, the Wilder-type pneumococcus was recovered from the sputum of C. T., who did not, however, develop a new pneumonic involvement.

Case 4. A man, suffering from Type 1 pneumococcus pneumonia, was treated on the 6th day of his illness with sulfapyridine and serum. He developed a pericarditis and a Type 1 pneumococcus empyema. The empyema was drained, and the temperature and pulse fell to normal. The temperature then rose to 103°F. and a purulent pericardial effusion from which *Streptococcus hemolyticus* grew was found. The patient was aspirated when there were signs of cardiac tamponade. He died the same day. Although the source of the hemolytic streptococcus could not be ascertained, the complication undoubtedly represented a cross-infection.

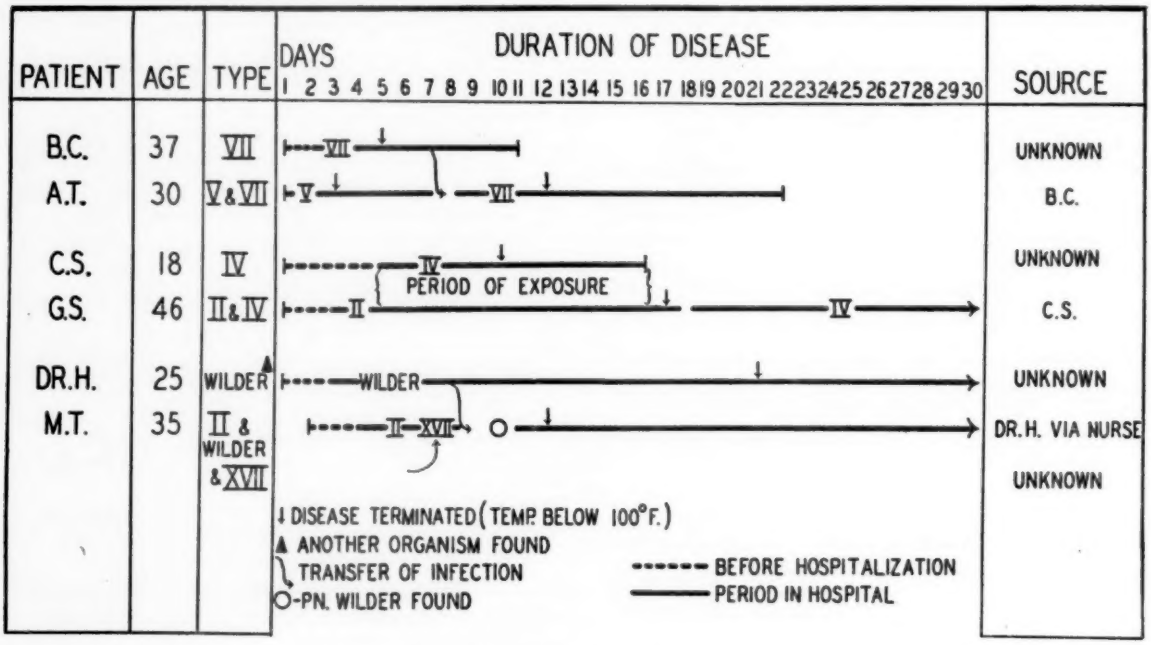
PATIENT
AGE
TYPE
DAYS
DURATION OF DISEASE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
SOURCE
B.C. 37 VII UNKNOWN
A.T. 30 V & VII B.C.
C.S. 18 IV UNKNOWN
G.S. 46 II & IV C.S.
PERIOD OF EXPOSURE
DR.H. 25 WILDER UNKNOWN
M.T. 35 II & WILDER & XVII DR. H. VIA NURSE
UNKNOWN
↓ DISEASE TERMINATED (TEMP. BELOW 100°F.)
▲ ANOTHER ORGANISM FOUND
TRANSFER OF INFECTION
O-PN. WILDER FOUND
BEFORE HOSPITALIZATION
PERIOD IN HOSPITAL

Figure 2. *Hospital-Ward Infections.*
The "Wilder" pneumococcus is now known as Type 33.

The first two of the cases just described were selected because they represent tandem infections in pneumonia patients, in which exacerbation of temperature and extension of the lesion would not have been correctly interpreted without the bacteriological studies that were undertaken. Previous bacteriological examination of the sputums and throat cultures failed to reveal the organisms which were found after exposure to known sources and which induced infection. Case 3 illustrates the possibility of spread by a vector, — the nurse, — and Case 4 a disaster that followed secondary infection with *Str. hemolyticus.*

Conclusions

Pneumonia is a communicable disease.

Patients suffering or convalescing from pneumonia due to a given type of pneumococcus may become infected by pneumococci of other types or by other organisms if an aseptic technic is not maintained.

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HODGKIN'S DISEASE[1]

Report of a Case with Unusual Longevity and Invasion of the Heart and Pericardium

MAX RITVO, M.D.*

BOSTON

THE purpose of this communication is to report a case of Hodgkin's disease that presented two unusual features. First, the patient survived a very long time, seventeen years having elapsed from the date when enlarged lymph nodes were first noted in the neck until death ensued. Secondly, at the post-mortem examination it was found that the pericardium and the heart were involved; the process had extended directly through the cardiac wall, and a mass measuring 1.0 by 1.5 by 1.5 cm. had projected into the lumen of the right auricle. In view of the rarity of invasion of the heart in Hodgkin's disease, it was deemed worthwhile to record this case.

CASE REPORT

The patient was a white, married woman. In 1920, when 32 years of age, she noticed a large swelling in the right side of the neck. She had borne two children and had had a subsequent miscarriage. The family and past histories were noncontributory. In July, 1922, she again became pregnant and the mass in the neck began to increase in size; a somewhat smaller but similar mass appeared on the left side. In November, 1922, 150 mg. of radium screened with brass and 2.5 cm. of wood was applied to the right supraclavicular region for 6 hours and to the left side for 2 hours. The enlarged lymph nodes diminished markedly but did not disappear entirely.

During the last 3 months of pregnancy, the cervical nodes increased greatly in size, and others appeared in the axillas and groins; the patient complained also of marked substernal pressure, dyspnea and a severe dry cough. The advisability of terminating the pregnancy was discussed, but the patient insisted on going to term, and was delivered of a normal baby girl in March, 1923. When she was seen the following month, large masses of lymph nodes were visible and palpable in both supraclavicular regions, the neck, the axillas and the groins. The spleen could be felt at the level of the iliac crest and extended across the midline. The liver was moderately enlarged. The right knee and leg were swollen, and there was severe pain radiating down both legs. The dyspnea, cough and substernal pressure had increased, and there was marked weakness. X-ray studies of the chest revealed a dense, uniform mass 7 by 5 cm. extending into the right midchest from the root of the lung. X-ray therapy was administered in April and May, 1923. Judged by modern standards, the dosage was small. Ten-minute exposures were given, each consisting of 8 milliamp. at 140 kv., with 4 mm. of aluminum filtration and a 40-cm. target-skin distance. The neck, chest, spleen and groins were irradiated, each area receiving two exposures; treatments were given at intervals of 2 or 3 days. The response was prompt, and the nodes soon disappeared almost completely. The spleen and liver were no longer palpable, and the pain, cough and dyspnea were relieved.

The patient was next seen in August, 1923, when examination showed a small swelling in the right side of the neck. No other nodes were found. The red-cell count was 5,400,000, with 85 per cent hemoglobin, and the white-cell count 7300, with 65 per cent polymorphonuclears, 25 per cent lymphocytes, 9 per cent monocytes and 1 per cent eosinophils. The platelets were normal. The patient looked and felt well, the only complaints being a vague sense of weakness and a tendency to easy fatigability.

In June, 1925, there was a recurrence, with a node 2 cm. in diameter in the right supraclavicular region and several smaller ones in the left side of the neck. X-ray films showed a definite increase in size of the right hilar nodes. X-ray therapy was given as previously, again with definite improvement. Neither a general nor a local unfavorable reaction followed the treatment. The patient's health and weight became excellent, and she was able to carry on all her usual duties as a housewife.

In January, 1927, and again in September and December of that year, four x-ray treatments were given to the neck and right side of the chest because of local recurrences. There was slight nausea and loss of appetite; these ill effects were of short duration, and the response to x-ray therapy was good. Thereafter the patient was observed at frequent intervals, but required no treatment until September, 1929, when the recurrence was slightly severer than previously. The node in the right neck measured 2 by 3 cm. and was very firm. The mass in the right chest extended from the level of the second rib to that of the fifth rib anteriorly, and from the mediastinum to the midclavicular region. The trachea was deviated to the left. Response to x-ray therapy was again good.

From 1930 to 1935, there were recurrences at intervals of several months, with a gradual lessening of the response to treatment. The voltage was 185 kv., with a 0.5-mm. copper filter, 200 r being administered at each exposure. The patient's general condition remained good throughout this period. She was not confined to bed at any time and continued with her usual duties, except that she required more rest.

In the latter part of 1935 and during 1936, the patient gradually failed. The nodes in the neck and mediastinum enlarged markedly, and there was increasing loss of weight, together with dyspnea, cough, poor appetite and weakness. Hospitalization became necessary and she was admitted on November 10, 1936. X-ray treatments of 200 r each were given daily (4 milliamp. at 200 kv., with a 40-cm. distance and a filter of 1 mm. of copper and 1 mm. of aluminum, over a 10-by-10-cm. field). At no time was an erythema produced. The entire chest and neck, however, assumed a deep tan, and several fine

*Assistant professor of roentgenology, Harvard Medical School; visiting physician, X-Ray Department, Boston City Hospital.

telangiectases appeared over the right side of the neck and chest. Symptomatic improvement resulted, and the nodes diminished somewhat. This improvement was of short duration, however, and in the spring of 1937 the patient became much worse. The weakness increased, and there were orthopnea, severe cough, hoarseness and loss of weight. The blood showed severe secondary anemia. In addition, gradually increasing cyanosis and congestion of the face, neck and upper extremities developed. Severe mental depression became a disturbing factor, with fits of weeping and melancholia that were particularly striking because the patient had previously been active, happy and optimistic.

X-ray treatment, sedation and oxygen therapy were unavailing, and the patient died on June 14, 1937.

Autopsy. The body was that of an adult woman showing fair development and poor nourishment. Enlarged peripheral lymph nodes were present in the left axilla. There was no clubbing of the fingertips. The skin of the anterior aspect of the chest was purple and adhered to the underlying tissues, this change involving a triangular area with its apex at the suprasternal notch and the base about 7 cm. lower. The skin and underlying tissues were peeled from the chest with difficulty and contained a firm, infiltrating mass that measured 3 cm. in thickness. The first and second ribs on the left and the upper three ribs on the right were involved in the process and were of the same consistence as the tumor.

The superior portion of the anterior mediastinum was markedly thickened and adherent to the chest wall. The tumor above described extended directly from the mediastinum, and it was impossible to determine any line of demarcation between the chest wall, the right pleural cavity, the right lung and the mediastinum. On the left side, there were a few extensions of the growth between the pericardium and the left parietal pleura. The right pleural cavity contained 1100 cc. of greenish-yellow cloudy fluid, and in the left pleural cavity there was about 350 cc. of similar fluid.

The tumor extended into the neck, but exactly how far could not be determined. The esophagus and descending aorta were compressed backward but were not actually invaded by the tumor. The trachea appeared surrounded by the growth. No space was found between the visceral and parietal portions of the pericardium.

When the heart was opened, a tumor mass measuring 1.5 by 1.0 cm. was found extending through the cardiac wall and projecting into the lumen of the right auricle. The orifice of the superior vena cava was markedly compressed, barely admitting a small probe. The narrowed lumen of the vein continued through the tumor mass for a distance of about 6 cm. and then was completely occluded by the growth. The azygos system was dilated, and a fresh antemortem clot was present in one of the azygos veins. The left pulmonary artery was normal. The right pulmonary artery was markedly compressed at a point 4 cm. from the bifurcation, the lumen barely admitting a fingertip. The left common carotid and left subclavian arteries were displaced and encircled by neoplasm. The left innominate artery was also completely surrounded by tumor at its origin. The lumen of the right subclavian vein was narrowed, and the smaller branches of this vessel were thrombosed. The heart measurements were as follows: T.V. 11.5 cm., P.V. 8.0 cm., M.V. 8.0 cm., A.V. 10.3 cm., R.V. 1.4 cm. and L.V. 4.0 cm. The tumor ended at the heart border, except in the area where it entered the right auricle.

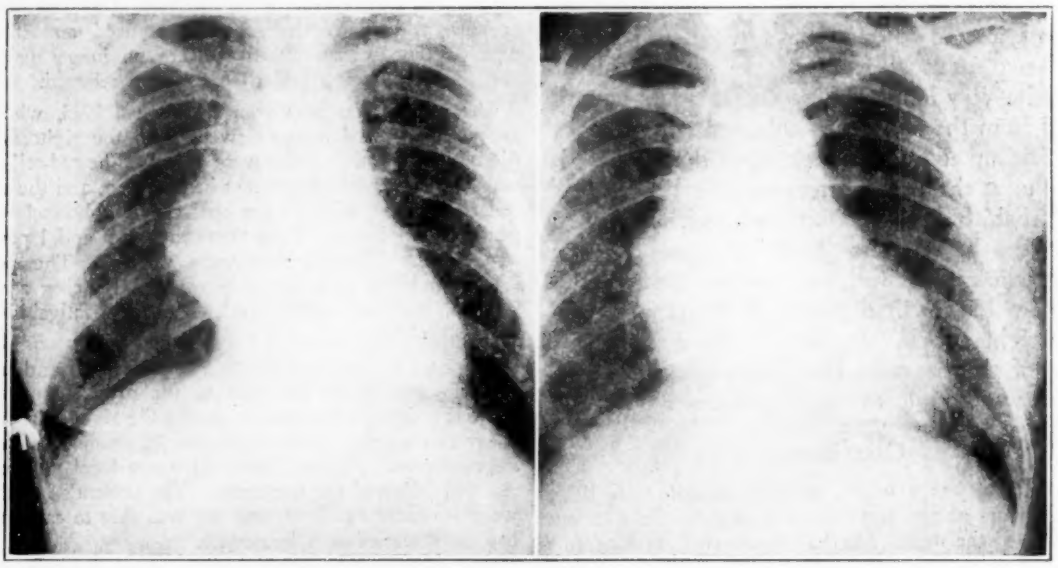

FIGURE 1. *Roentgen Films of the Chest Taken in 1927 (left) and 1930 (right). The mediastinal mass projects into the right mid-lung field.*

The mass in the chest in its entirety measured 15 by 15 cm. Serial sections revealed a dense, firm, white growth which did not pit and which cut with a gritty sensation. The left lung could be separated from the mass, but the medial border of the right lung could not be demarcated because the densely infiltrating growth involved the entire medial half.

The spleen weighed 140 gm. and was normal in shape. The gastrointestinal tract revealed no abnormalities. The liver weighed 1320 gm. and appeared normal in shape and consistence. The gall bladder, kidneys and adrenals were not remarkable.

Two of the sections of heart were taken from regions where the tumor had invaded the auricular musculature. These areas showed tumor masses projecting into the

auricle but not covered by endothelium. In places the tumor was extremely cellular, but in others it had undergone necrosis and fibrosis. The cellular areas were composed of an abundant stroma of fibrous tissue in which a variety of cells were present. There were many eosinophils and a number of monocytes with numerous large cells, irregular in shape, containing vesicular nuclei and prominent dark nucleoli and many multinucleated giant cells. In a central portion of the tumor there was a small spicule of bone. The cells infiltrating the myocardium were similar in appearance to those making up the bulk of the tumor.

One section of lung revealed a large area of invasion by tumor, parts of which were converted into collagenous tissue. Other regions were cellular and showed a picture similar to the tumor that had invaded the heart. At the transition between the tumor and lung, groups of cells were seen breaking through the alveoli and producing small patches of ulceration. The second section contained an extensive area that appeared to have been tumor but was undergoing degeneration and fibrosis. Most of the remaining portion of this section consisted of lung tissue, the markings of which had been obliterated by fibrin and scattered polymorphonuclear cells. The rest of the lung showed a moderate to marked edema, with congestion of the capillaries.

Two sections taken from the mediastinal mass were studied. In one, degeneration and fibrosis had occurred to such a degree that a histological diagnosis was impossible. Essentially, the picture was one of degeneration and fibrosis, with moderate cellularity consisting chiefly of what appeared to be monocytes and irregular, undifferentiated cells. The second section of tumor contained striated muscle and large areas of tumor similar to those described in the previous section.

No tumor invasion was found in the liver. The firm demarcated area, seen grossly in the spleen, was found microscopically to consist chiefly of fibrosis.

The pathological diagnosis was as follows: Hodgkin's disease, involving the mediastinum, lung, heart, pericardium, chest wall, axillary nodes and subcutaneous tissue; postradiation fibrosis; obstruction of the superior vena cava; thrombosis of the azygos vein; bilateral hydrothorax.

It is known that Hodgkin's disease may occasionally run a relatively benign and very prolonged course. Gilbert[1] cites cases that lasted twenty years and more. Jackson[2] reports a case in which the involved nodes were removed surgically with no recurrence after a lapse of twenty-six years, and another in which the patient survived for sixteen years. Although not unique in respect to longevity, the case here reported is extremely rare.

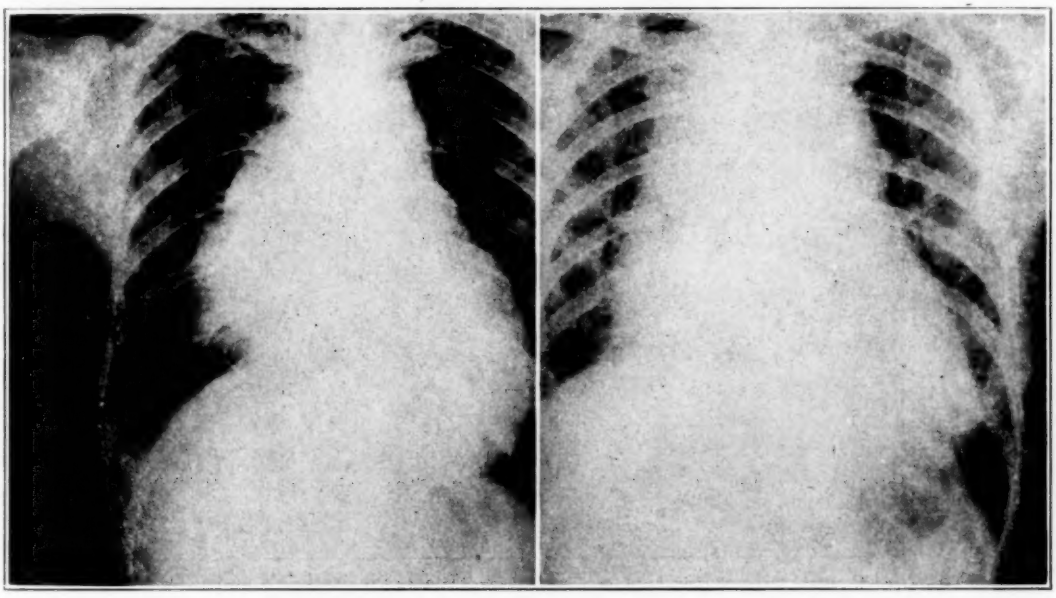

Figure 2. ***Roentgen Films of the Chest Taken in 1935 (left) and 1937 (right). Note the marked increase in the size of the mass in the last film.***

The prognosis in Hodgkin's disease is poor, the average period of survival being only two and a half to three years. Jackson[3] recently reviewed this subject and summarizes the present knowledge as follows:

> In Hodgkin's disease, we find the most interesting data as to prognosis. The average duration of life from the first symptom in Hodgkin's lymphoma is two and a half years; yet nearly 30 per cent survive five years or longer, and nearly 20 per cent ten years or longer. In contrast, the average case of Hodgkin's granuloma lasts but a scant two and a half years and very few patients survive for over ten years; nearly three quarters are dead within three years. No person with Hodgkin's sarcoma has in our experience survived a three-year period.

As the case here recorded is a Hodgkin's granuloma, the duration of life in the light of Jackson's statement is distinctly unusual.

It is generally agreed that in most cases treatment prolongs life for only a short while. The chief benefits resulting from therapy, particularly with the x-ray, are temporary shrinkage or complete disappearance of the involved nodes and the enlarged spleen, with consequent relief of pressure and the amelioration of other distressing symptoms. In consequence, the patient is often restored to good health for relatively long periods and is usually enabled to carry on practically all normal activities during these intervals. Occasionally a patient with an extensive and apparently severe form of the disease lives in comparative comfort for a long time, as in the present case. It is impossible to determine in advance, either on the basis of clinical experience or by any known test, which case will progress favorably and which will fail to respond to therapy. Therefore, every patient with Hodgkin's disease should be given the full benefit of early, thorough and persistent x-ray therapy.

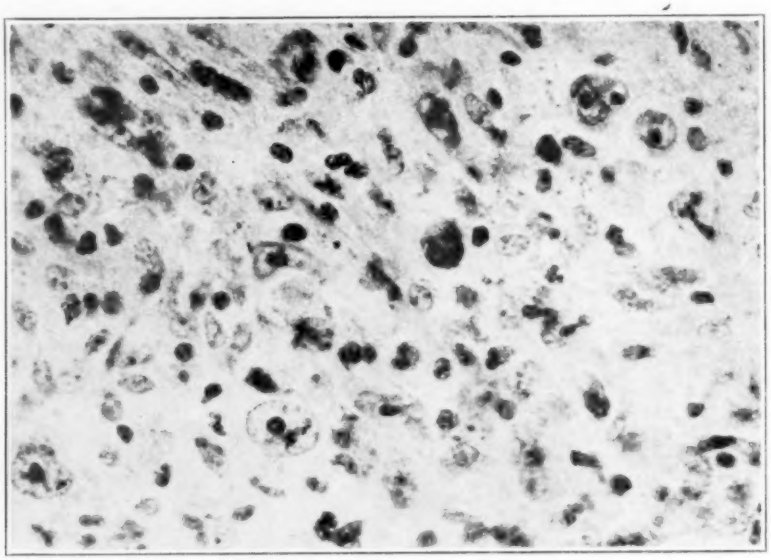

FIGURE 3. *Photograph of a Section through the Central Portion of the Tumor.*

In Hodgkin's disease, the involvement is primarily in the lymphoid structures, although infiltrations may occur in practically every tissue and no part of the body appears to be entirely immune. However, cardiac and pericardial lesions are very rare, and these organs are among the least commonly involved.

Hodgkin,[4] in his first observations of the condition which now bears his name, noted that the disease was not confined to the lymphoid tissues alone, and in 1869 Murchison[5] cited a case of "lymphadenoma" in which the liver, lung and heart, as well as the lymphatic system, were involved. Gowers[6] in a comprehensive study in 1879 indicated that the pericardium and heart muscle could be involved in this condition. Despite these early reports, many of the modern texts and treatises on Hodgkin's disease either make no reference to the possibility of cardiac invasion or note it only very briefly. Longcope[7] states that although there may be cardiac displacement from the mediastinal masses, the heart itself is not involved in the disease. Ewing[8] mentions that extensions to the heart have been noted. A few scattered references are found in the recent literature. Yates and Bunting[9] described a case that involved the visceral pericardium. McAlpin[10] in a review of the Presbyterian Hospital (New York City) records found myocardial nodules in 2 cases, involvement of the pericardium in 1, and a lesion of the pericardium in 1. In the "Case Records of the Massachusetts General Hospital,"[11] a case of Hodgkin's disease involving the pericardium is cited. Harrell[12] reports an unusually interesting case in which he found a dense zone of Hodgkin's tissue extending into the pericardium, epicardium and myocardium. He also reviews 8 cases that he collected from the literature; of these, there was 1 with small masses in the epicardium, the remainder revealing involvement of the pericardium.

Invasion of the heart and pericardium in Hodgkin's disease is therefore a very rare occurrence.

as evidenced by the small number of cases recorded in the literature. The reasons for this are not clear. The relatively small amount of lymphoid tissue in the heart is doubtless an important factor. Harrell[12] believes that pericardial involvement may take place by retrograde extension through the lymphatics or by way of the blood.

The lesions in Hodgkin's disease may undergo a malignant degeneration, with the formation of a sarcoma. In the case herein recorded, however, there was no sarcomatous metamorphosis, the pericardial and cardiac involvement being by a granulomatous Hodgkin's lesion. No definite clinical or x-ray indication that the heart had been invaded was present during the patient's illness, the diagnosis being made post mortem. Since cardiac invasion is necessarily of the gravest prognostic import, it is of great interest to the clinician, roentgenologist and pathologist. If this possibility is borne in mind, the diagnosis can be correctly made — in some cases, at least — on the basis of the clinical and x-ray evidence.

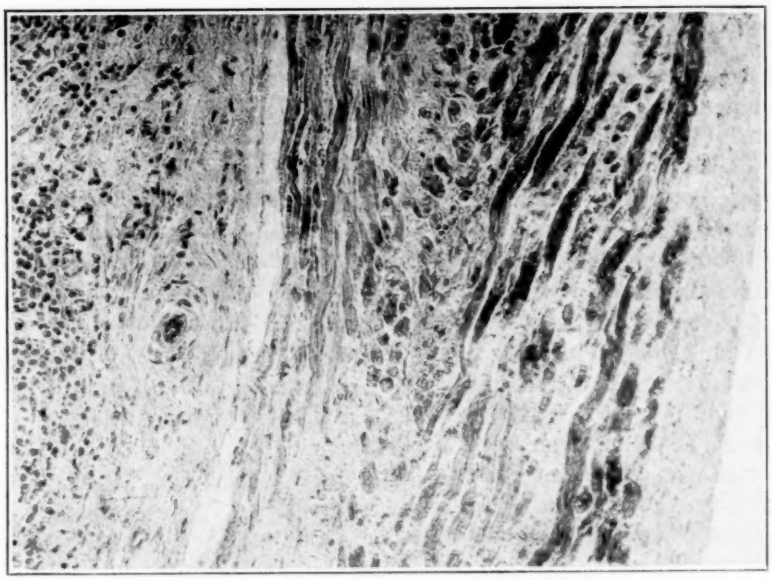

FIGURE 4. *Photograph of a Section Showing Invasion of the Heart Muscle.*

SUMMARY

A case of Hodgkin's disease presenting two very striking features is reported. First, the duration of the disease was seventeen years, an unusual longevity. Secondly, the patient at autopsy showed involvement of the pericardium and direct invasion of the heart by a mass projecting into the right auricular cavity.

In the case herein recorded, the prognosis appeared grave early in the disease because of the severe condition and the extensive involvement. Yet under x-ray therapy the patient survived an unusually long time, was well for long periods, and did not suffer greatly until near the end. Hence, early, persistent and thorough x-ray therapy is indicated in every case.

485 Commonwealth Avenue

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MASSACHUSETTS MEDICAL SOCIETY PRIZE ESSAY

MULTIPLE PULMONARY THROMBI ASSOCIATED WITH CYANOSIS AND RIGHT-SIDED CARDIAC HYPERTROPHY*

Report of a Case

Victor G. Balboni, M.D.†

BOSTON

IN 1901 Abel Ayerza, then professor of medicine at the National University of Argentina, described in an unpublished lecture a condition termed *"cardiacos negros."* This syndrome was characterized by cyanosis, dyspnea, polycythemia, right-sided cardiac hypertrophy and eventually death in cardiac failure.[1] Clubbing of the fingers, cephalalgia, vertigo, somnolence and occasionally hemoptysis have since become well-recognized components of this syndrome. Twelve years later Ayerza's pupil, Arrillaga,[2] correlated the clinical picture with the pathological finding of arteriosclerosis of the pulmonary vessels. This he believed was the end result of chronic pulmonary diseases such as asthma, chronic bronchitis, tuberculosis, or pleural adhesions, all of which produced pulmonary emphysema. With the demonstration of syphilis of the pulmonary arteries by Warthin[3] and Escudero,[4] Arrillaga later came to consider syphilis the chief cause of pulmonary arteriosclerosis and its syndrome of *cardiacos negros*. Although many authors[1, 5–9] are in agreement concerning the syphilitic etiology of pulmonary arteriosclerosis, it is now generally believed that syphilis is responsible for relatively few of these cases.[10–12]

Posselt[13] in 1909 and later others[11, 14, 15] have classified pulmonary arteriosclerosis into primary and secondary forms, according to whether the sclerosis developed from disease primary in the vessels themselves or was secondary to some other factor producing elevation of pulmonary pressure.

As so classified, primary pulmonary arteriosclerosis can be produced by syphilis of the pulmonary arteries, although this is probably a less frequent cause than it was previously supposed to be.[10, 11] Extensive diminution in the size of the lumens of the pulmonary vessels has also been reported following influenza, rheumatic fever, certain allergic diseases and schistosomiasis of the pulmonary arteries.[11, 16–20] In most cases the etiology is obscure. In all the above-mentioned conditions, the process is thought to be an endarteritis obliterans affecting chiefly the small arterioles.[10, 11, 21]

Secondary sclerosis of the pulmonary arteries is the commoner type. In this form, the process is thought to be an atherosclerosis of the large arteries resulting from conditions producing an elevated pulmonary arterial pressure such as chronic asthma, tuberculosis, pulmonary fibrosis, carcinoma of the lung, pleural adhesions, mitral heart disease, patent septal defects in the heart, patent ductus arteriosus and, last and probably least, frequently multiple pulmonary emboli.[11, 14, 15, 22, 23] However, in an exhaustive study of the pulmonary and vascular changes in mitral stenosis Parker and Weiss[24] have shown not only that the large vessels are affected, but also that the small arteries show intimal thickening, and that this may go on to vascular occlusion. These changes, though rarely sufficient to produce a complete Ayerza's syndrome, undoubtedly play an important role in the degree of cyanosis accompanying mitral stenosis.

Thus we see that there is no one cause of the Ayerza's syndrome. The following case is significant because the literature contains, in so far as I know, only four reports[25–28] of the syndrome following multiple thromboses of the smaller pulmonary vessels without marked arteriosclerosis or arteriolarsclerosis.

Case Report

A 66-year-old Greek laborer entered the Peter Bent Brigham Hospital on January 28, 1939, because of dyspnea, cyanosis of the face and swelling of the face and legs of 3 weeks' duration. The family history was noncontributory. The patient had been well and strong all his life. There was no history of heart or lung disease other than influenza 21 years before entry. Two previous hospital admissions, both in 1932, were for a bilateral herniorrhaphy and the treatment of hypertrophic arthritis. Six years previous to admission the patient entered the Out-Door Department complaining of puffiness under the eyes. The blood pressure at that time was 140/80, and the basal metabolic rate +5 per cent. Three years before hospitalization he first noted some dyspnea on exertion. However, this was not troublesome until 20 months before death, when he again came to the Out-Door Department, this time complaining of marked swelling of the legs. The heart was found to be moderately enlarged to the left, the neck veins were distended, and there was marked pitting

*Last spring the Massachusetts Medical Society offered a prize of fifty dollars for the best-written and most comprehensive case report submitted by an intern in any Massachusetts hospital approved by the American Medical Association for intern training. The competition closed on May 5. Six case reports were submitted, and a committee, consisting of the president of the Boston Medical Library, the editor of the *New England Journal of Medicine*, and the chairman of the Committee on Medical Education and Medical Diplomas of the Massachusetts Medical Society, served as judges. The prize was awarded to Dr. Victor G. Balboni.

†Formerly, intern in pathology, Peter Bent Brigham Hospital; medical house officer, Massachusetts General Hospital.

edema of the legs and lower abdominal wall. No cardiac murmurs were heard, the rhythm was regular, and the blood pressure was 130/90. On digitalis and a low-salt and high-vitamin diet the edema disappeared and the heart appeared to decrease in size. For the next year the patient felt well except for slight substernal distress on exertion. Three weeks before admission he came to the Out-Door Department complaining of cyanosis of the face and edema of his face and legs. In spite of bedrest these symptoms gradually increased, and on entry he was found to be quite ill and somnolent, though alert when aroused. The face, hands and feet were cyanotic in both the recumbent and the sitting position. The neck veins were found to be moderately distended, and the heart extended 11.5 cm. to the left of the midsternal line and 5.0 cm. to the right. The cardiac rate was 106, the rhythm was regular, no murmurs were heard, and the blood pressure was 135/80. Respirations were 28 and not labored. Coarse, moist rales and rhonchi were heard throughout both lung fields. The fingers were slightly clubbed. Vision in both eyes was limited to the differentiation of light and dark. The deep reflexes were not remarkable, and the pupils reacted poorly to light.

FIGURE 1. *Organized Thrombus in Process of Canalization. Section taken from right upper lobe and stained with eosin and methylene blue (×275).*

The laboratory findings were as follows. The red-cell count was 6,500,000, the white-cell count 17,500 and the hematocrit reading 61.5 per cent. The total protein was 4.5 gm. per 100 cc., and the nonprotein nitrogen 54 mg. The urine showed a specific gravity of 1.022, with no red blood cells, rare white blood cells and an occasional hyaline cast. The right antebrachial venous pressure was 203 mm. of water, and the right femoral venous pressure 162 mm. The femoral arterial blood was 65.6 per cent saturated with oxygen, and the femoral venous blood was 9.37 per cent saturated. Electrocardiographs revealed no preponderance of either ventricle. A blood Hinton test was negative. The spinal fluid was under an initial pressure of 270 mm. of water and contained 270 red blood cells per cubic millimeter.

Oxygen given by intranasal catheter failed to relieve the cyanosis appreciably, and in spite of digitalis and supportive treatment the patient continued to fail. During the last 5 days of life the pulse was weak and extremely variable, showing extrasystoles and paroxysms of tachycardia. He became more and more cyanotic, the respirations became shallower, and death occurred on the 14th hospital day. A diagnosis of Ayerza's syndrome was made before death on the basis of cyanosis, polycythemia, cardiac hypertrophy with marked enlargement of the right side, slight clubbing of the fingers and somnolence. The low oxygen saturation of the blood, in the absence of a congenital defect in the heart producing a right-to-left shunt, and the failure to respond to oxygen were proof of a block between the alveolar air and the pulmonary circulation. The spinal-fluid findings suggested a subarachnoid hemorrhage.

Autopsy. A post-mortem examination was made 14 hours after death. The body was that of a markedly cyanotic, well-developed and moderately well-nourished man and showed a moderate amount of pitting edema of the ankles, extending superiorly to the midportion of the tibias. There was slight clubbing of the fingers, and in each inguinal region there was a well-healed herniorrhaphy scar.

The liver and spleen showed passive congestion but were otherwise not remarkable. The prostate, which was rubbery and firm in consistence, showed moderate symmetrical enlargement. The aorta and tributaries showed a minimal amount of arteriosclerosis, and their elasticity was well preserved.

The heart weighed 530 gm. The pericardium was adherent to the anterior surface of the right ventricle by several fibrous adhesions. Beneath these adhesions there was a small area of calcification in the epicardium of the right ventricle 1.5 cm. below the coronary sulcus, measuring 1.5 x 1.0 cm. and less than 1 mm. in thickness. As studied in situ the heart was enlarged both to the left and to the right, although the enlargement on the right side was by far the more striking. The right ventricular myocardium measured 15 mm. in thickness, the left ventricular myocardium 23 mm. Except for the cardiac hypertrophy, both gross and microscopic examinations of the heart were essentially negative. No ante-mortem thrombi were present in the ventricles, atriums or their appendages, and the coronary vessels showed no appreciable atheromatous change.

Gross examination of the kidneys revealed several small, wedge-shaped areas of cortical infarction, each measuring 3 mm. in width. Microscopically in these infarcted areas several moderately large arteries were found that were occluded by fibrinous thrombi exhibiting early peripheral organization. No noteworthy degree of arteriosclerotic changes was present in the vessels throughout the renal parenchyma, and except for the small infarcts, the kidneys were essentially normal.

The brain weighed 1470 gm., was symmetrical and revealed no blood on or beneath the dura mater or pia-arachnoid. Both occipital lobes were soft to palpation, and their convolutions slightly flattened. This softening extended anteriorly from the occipital poles for approximately 5 cm., and laterally from the longitudinal fissure on each side for 5 cm. Coronal sections revealed the softening on the right to be roughly spherical, measuring 5 cm. in diameter and involving the entire tip of the occipital lobe except for its inferolateral border. It extended anteriorly to the level of the sylvian fissure in the inferomedial aspect of the occipital lobe. On the left, the softening involved the entire white matter of the occipital lobe for a distance of 4 cm. The ventricles were symmetrical, free

from hemorrhage and not distorted. Microscopically, in the substance of both occipital lobes occasional small arteries were found to be occluded by fibrinous thrombi. The Virchow–Robin spaces were dilated and engorged with red cells, and the brain substance surrounding these vessels showed marked destruction and infiltration by polymorphonuclear leukocytes and mononuclear phagocytes. The remainder of the brain was not remarkable except for a moderate degree of intimal thickening of the arteries.

The right lung weighed 1140 gm., the left 420 gm. The

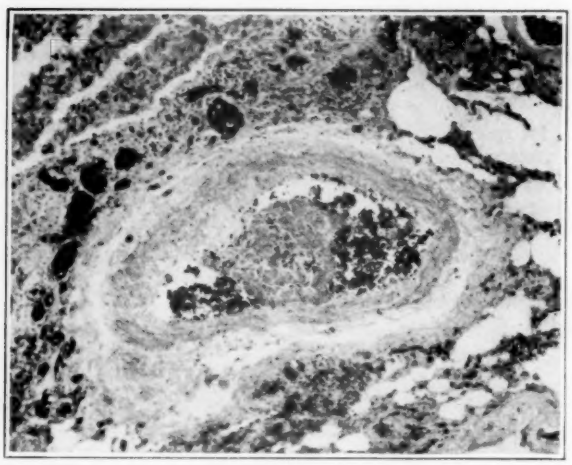

FIGURE 2. *Organized and Canalized Artery.*
Section taken from right upper lobe and stained with eosin and methylene blue (×90).

right superior lobe was bound firmly to the posterior and lateral parietal pleura by dense fibrous adhesions. Both the superior and inferior lobes on the left were adherent to the mediastinum, and the superior lobe was also adherent at its apex and along its posterior and lateral aspects to the parietal pleura. The superior lobes on the right and left were gray and crepitant to palpation; the inferior lobes were reddish gray and revealed little crepitus. There was an area of consolidation measuring 5 by 6 cm. on the anterior surface of the right inferior lobe that was found to be a well-encapsulated abscess. Much sanguinous fluid exuded from the cut surface of both lungs, but no grossly purulent fluid except from the previously mentioned abscess. No other areas of consolidation were noted. The pulmonary arteries were opened to their third ramification, and no thrombi were found. Occasional yellow plaques, none of which were ulcerated or calcified, were noted in these vessels. On close examination of the cut surfaces of the lungs many small vessels, measuring 2 mm. and less in diameter, were found to be occluded by dark-red thrombi. The bronchi contained considerable serosanguinous fluid. For microscopic study sections were made from thirty blocks of lung tissue taken from all portions of the lungs and stained with eosin and methylene blue, by Weigert's elastic-tissue method, with hematoxylin and eosin and with aniline blue. A considerable increase of fibrous tissue was noted about the bronchi and blood vessels and in the alveolar walls. The most marked pathologic changes were found in the small arteries of the lungs and in the alveolar walls supplied by these vessels. Throughout all lobes many of the arteries varying from 0.1 mm. to 2.0 mm. in diameter were occluded by thrombi. These were of various ages, some being completely organized and canalized (Figs. 1, 2 and 3), while into others only a few fibroblasts had extended from the vessel wall (Fig. 4). The most recently formed thrombi were found in the vessels measuring 0.2 to 0.4 mm. in diameter. Frequently the thrombi appeared to be propagating in a retrograde manner into the larger vessels (Fig. 5). It was interesting that no thrombi were noted in the vessels measuring 0.09 mm. and less in diameter. These smaller vessels did show, however, concentric thickening of their walls such as is commonly seen in the kidneys in hypertensive disease. Splitting of the internal elastic lamina and intimal thickening were not pronounced in the thrombosed vessels, being no commoner than is customary in a person of corresponding age. There was no leukocytic infiltration of the vessel walls. In a patchy distribution throughout all lobes, and corresponding roughly to the distribution of the thrombosed arteries, there were groups of alveoli that showed considerable fibrous thickening of their walls. These thickened walls were practically avascular, and occasionally the lining epithelium had undergone metaplasia, becoming low cuboidal in type. In the lower lobes many of the more normal alveoli showed marked capillary engorgement and pericapillary edema.

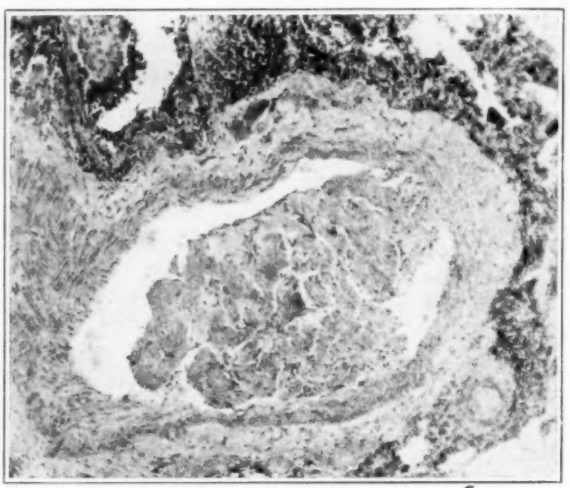

FIGURE 3. *Organized and Canalized Artery.*
Section taken from left upper lobe and stained with hematoxylin and eosin (×85).

Occasional alveoli contained a few "heart-failure" cells. There were also several true infarcts, only one of which was macroscopic in size; this had broken down, forming the previously mentioned abscess. The lower lobes bilaterally revealed a mild degree of bronchopneumonia, which was most marked in the right lower lobe.

A satisfactory pathogenesis of the predominating lesion, namely, a propagating thrombosis with organization and canalization of the pulmonary vessels, is not apparent. That these lesions were on a nonspecific infectious basis cannot be definitely excluded because of the peribronchial fibrosis. There was, however, no history of chronic bronchitis. Although Moller[22] believes that it is possible to differentiate histologically autochthonous thrombi from emboli, an attempt to make such a distinction in this case forces one to agree with Brenner[11] that this is quite impossible. Arteriosclerotic changes in the pulmonary vessels were no

more extensive than was compatible with the patient's age, and there was no evidence of arteritis or endarteritis obliterans. No sources from which emboli could have arisen were found in the body, although it must be emphasized that the arms and legs were not dissected. There was no clinical evidence of thrombi in these regions.

The hypothesis entertained in this case is that spontaneous thromboses occurred in the small vessels throughout the lungs. After the formation of the thrombi the sequence of events leading to the morphologic changes in the lungs is more readily understandable. Following pulmonary-artery thromboses usually one of the following phenomena occurs. Either the lung tissue involved breaks down and is eventually replaced by scar tissue, or, if the pulmonary venous pressure is not appreciably increased, a small collateral circulation, probably from the bronchial arteries, maintains the alveolar walls intact. However, under the latter circumstances the alveolar walls are relatively avascular, and rapidly develop a marked increase of collagenous fibrous tissue, which separates the capillaries from the alveolar basement membrane. This fibrous thickening of the alveolar walls prevents free exchange of gases between the alveoli and their capillaries, and the functionless respiratory epithelium of the alveoli becomes low cuboidal in type.

FIGURE 4. *Thrombosed Vessel Showing Organization. Section taken from right lower lobe and stained with eosin and methylene blue (×155).*

As the above-described lesions spread through the lungs in question, the pulmonary vascular bed was reduced. Pulmonary arterial hypertension, right-sided cardiac hypertrophy and eventually cardiac failure followed in the order stated. With cardiac failure the capillaries, especially those in the lower lobes, became engorged, and pericapillary and alveolar edema occurred. All three of these factors hinder the free exchange of gases in the remaining normal alveoli. Thus, the marked reduction in oxygen saturation of the arterial blood is the expected physiologic concomitant of the described morphologic changes in the lungs, that is, arterial occlusions with marked reduction in the pulmonary vascular bed, fibrosis of the alveolar walls, capillary engorgement and pericapillary and alveolar edema.

The cerebral and renal thrombi may conceivably also have arisen in situ or may have been emboli from thrombosed pulmonary vessels that in actuality were veins, because, as Mallory[29] has pointed out, differentiation of small arteries and veins of the lung is frequently impossible.

SUMMARY

A case of marked cyanosis, right-sided cardiac hypertrophy and cardiac failure in a man without known pre-existing heart disease is presented. Because of the markedly reduced oxygen saturation of the arterial blood in the absence of evidence of a right-to-left-sided vascular shunt in the heart, and the failure of the cyanosis to respond to intranasal oxygen, a block between the alveolar air and the pulmonary vascular bed was postulated. Autopsy showed this to be due to apparently spontaneous multiple thromboses of the smaller pulmonary vessels. Similar thrombi were found in both the brain and kidneys.

FIGURE 5. *Fresh Thrombus in Moderately Large Vessel. Section taken from left lower lobe and stained with hematoxylin and eosin (×50).*

Various pathologic conditions that can produce Ayerza's syndrome are enumerated.

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REPORT ON MEDICAL PROGRESS

THE TREATMENT OF JUVENILE DIABETES MELLITUS

ALLAN M. BUTLER, M.D.*

BOSTON

THE recent advances in the knowledge of the abnormal physiology of experimental diabetes mellitus, which have been reviewed in earlier progress reports,[1] have altered profoundly concepts of the disease,[1-12] but as yet have not added to the therapeutic armamentarium that was available to the clinician four years ago. Present therapy is based almost entirely on the concepts of fifteen to twenty years ago concerning the derangement of carbohydrate,[13] salt and water metabolism,[14-17] and on the insulin provided by Banting and Best in 1922 and the protamine zinc insulin that followed Hagedorn's introduction of protamine insulin in 1935.[18]

The progress of the conflict between the proponents of low-carbohydrate and high-carbohydrate diets has remained veiled in the misty arguments of the past two decades and has only occasionally been visualized in the light of modern physiology and therapy. The clear-cut experiments of Conn and Newburgh[19] on the effect of iso-glucogenic quantities of protein and carbohydrate on the blood sugar have seemingly attracted little notice from either camp. The contributions of Lawrence and Archer[20] and Campbell and his co-workers[21] on the relation between diet and the action of protamine zinc insulin have provided impressive evidence of the effectiveness of this type of insulin in conjunction with low-carbohydrate intake but have not disturbed the clinician's allegiance to the cause of high-carbohydrate regimes.

TABLE 1. *The Relation between the Carbohydrate in the Diet and the Effectiveness of Protamine Zinc Insulin.*

TEST PERIOD	DAILY DIET: CARBOHYDRATE CONTENT	DAILY DIET: CALORIC CONTENT	DAILY DOSAGE OF INSULIN*	RANGE OF BLOOD SUGAR	RANGE OF GLUCOSE IN 24-HR. URINE
days	*gm.*	*cal.*	*units*	*mg./100 cc.*	*gm.*
10	160	±1800	10R–16P	70–180	3–14
12	100	±1750	0R–14P	70–180	<1– 3
8	125	±1800	0R–16P	125–210	7–39
10	125	±1800	4R–20P	90–190	2–19
5	190	±1900	10R–20P	80–230	12–27

*Given before breakfast. R=plain insulin; P=protamine zinc insulin.

A pertinent example is provided from the diabetic clinic of the Infants' and Children's Hos-

*Assistant professor of pediatrics, Harvard Medical School; assistant visiting physician, Infants' and Children's Hospitals.

pitals, Boston. The data in the accompanying table illustrate the increased effectiveness of protamine zinc insulin with a low-carbohydrate intake and the excellent control attainable on a low-carbohydrate, protamine insulin regime. Yet in spite of such evidence, I have continued for the simple, and perhaps invalid, reason of practical expediency to remain among the ranks of the many who prescribe diets that contain, according to the age of the patient, from 125 to 200 gm. of carbohydrate. Such diets are probably the most commonly used today. They require for adequate diabetic management of most juvenile* patients the use of both protamine zinc and plain insulin.†[1, 11, 21, 23–27] Even then, considerable glycosuria occurs after at least one meal each day, unless the insulin is given more than once daily. The fact that most authorities do not commonly employ another dose of plain insulin before the particular meal‡ that is followed by this glycosuria indicates that transient glycosuria and the daily urinary loss of between 5 and 15 gm. of glucose are in their opinion relatively harmless.[1, 11, 18, 21, 23, 24, 26, 27, 29, 30] For if this opinion were not held, patients should be on either a low-carbohydrate diet with protamine zinc insulin once a day, or a liberal-carbohydrate diet with protamine zinc insulin once and plain insulin twice daily.

Because almost perfect control in most cases may be provided by either of these procedures, there seems to be little reason for resorting to the elaborate and inconvenient regime involving multiple injections of plain insulin.[31] Moreover, the desirability of providing some protamine zinc insulin in the daily therapy is evidenced by the fact that transient ketosis, hypercholesterolemia and enlargement of the liver from excessive storage of glycogen are not encountered in patients receiving some insulin in this form.[25, 30, 32, 33] The early morning hyperglycemia that used to be so troublesome with plain insulin alone is easily controlled by the administration of a portion of the total insulin in the form of the protamine preparation.[1, 11, 18, 21, 23–27, 30, 33]

The early unfavorable experiences with the use of protamine insulin are seldom encountered today.[1, 11, 18, 21, 23–26, 29, 30, 33, 34] There is now a wider appreciation of the fact that Hagedorn[18] introduced the use of protamine insulin in conjunction with diets relatively low in carbohydrate and that protamine zinc insulin is relatively ineffectual in reducing the daytime glycosuria of patients on high-carbohydrate diets unless the protamine insulin is supplemented with adequate plain insulin. The realization that young children require a higher ratio of plain insulin to protamine insulin than do older patients has increased the effectiveness of combined therapy in the younger group. Consequently the administration of excessive doses of protamine insulin with continued glycosuria during the day and the occurrence of annoying headaches or of severe insulin reactions between 2 a.m. and breakfast has disappeared from current practice.

Thus, in this four-year interim, when the advances in scientific knowledge have not been applicable to the clinical treatment of diabetes, the clinician has learned much about the art of applying available knowledge. Knowing that all diabetic infants and children require insulin, he no longer attempts to determine "carbohydrate tolerance" by graded diets, but places the patient, as soon as possible, on a routine diet and then administers the amount of insulin required for adequate control. Whether the carbohydrate content of the diet is low or high, experience has shown the advantage of immediately prescribing a dose of plain insulin and one of protamine zinc insulin that is lower than that which would result in hypoglycemia during the next twenty-four hours, and of supplementing this with doses of plain insulin, as indicated by the urine-sugar, or if necessary, by the blood-sugar concentrations. Using the general principle that the protamine insulin should be used to control the early morning blood sugar and the plain insulin to control the blood sugar during the day, the clinician can determine, in the course of five or six days, the before-breakfast dose of each type of insulin required for the control of each patient. He is further guided by the knowledge that a low-carbohydrate diet requires little and possibly no plain insulin, whereas for a young child a liberal-carbohydrate diet usually necessitates approximately equal amounts of each kind of insulin. When using a regime of the latter type, he knows that 15 to 20 gm. of carbohydrate should be taken in the midmorning to prevent hypoglycemia before the midday meal. Once the patient is adjusted to the routine diet and the daily before-breakfast insulin therapy, the physician controls the minor fluctuations in sugar balance due to infection or to the emotional stresses and strains of everyday life by slightly increasing or decreasing the dosage of plain insulin. If, during a period of temporary imbalance, hyperglycemia persists for several days, so that urine specimens taken before supper show too much sugar, an in-

*The word juvenile is used not so much to designate the age group, as to indicate that this progress note is not concerned with the type of diabetes that in older people appears to result from a glycogenic dysfunction associated with adiposity.[22]

†"Plain insulin" is used to designate both amorphous insulin and crystalline insulin, since there appears to be no difference of clinical importance in the action of these two preparations.[28]

‡The evening meal, if the insulin is given before breakfast.

jection of from 4 to 8 units of plain insulin before the evening meal may be prescribed. Insulin so given is not only very effective in controlling temporary hyperglycemia, but also unlikely to cause serious hypoglycemia and the possible reactions, which accumulating evidence[35–38] indicates should not be considered lightly.

From these general considerations, the physician, to facilitate the patient's independent control of his diabetes, on the usual regime of liberal diet and both types of insulin before breakfast, provides some such rules of thumb as the following:

Symptoms of an insulin reaction between 10:30 a.m. and dinner in the middle of the day are the result of too little midmorning food or too much plain insulin. If reactions occur at this time and sufficient midmorning food is being taken, the dose of plain insulin should be reduced by 2 to 4 units, depending on the number of units taken before breakfast.

Symptoms of an insulin reaction between 2 a.m. and breakfast are the result of too much protamine zinc insulin and make it necessary to reduce the dose of protamine zinc insulin by 2 to 4 units, depending on the number of units taken before breakfast.

Reactions occurring late in the afternoon are the result of the combined effect of the plain insulin and the protamine zinc insulin — usually accentuated by exercise. When the diabetes is otherwise well controlled, they are best treated by giving midafternoon food in the form of fruit, fruit juice or bread, the last being taken from the bread of supper.

The appearance of too much sugar in the urine voided before the midday meal suggests the need of more plain insulin. However, before the dosage of insulin is increased, it is important to be certain that the sugar found in the specimen voided before the noon meal has not come into the bladder following breakfast. To make sure of this, it is necessary that the bladder be emptied some time between 10 and 11 a.m. If such a voiding has occurred, the sugar that appears in the urine before the noon meal is a fair index of the inadequacy of the dosage of plain insulin, which should then be increased by no more than 2 to 4 units at a time.

Too much sugar in the urine before breakfast suggests the need of more protamine zinc insulin. However, before sugar in the urine at this voiding is considered as an indication for increasing the dose of protamine zinc insulin, the possibility that this sugar might have come into the bladder the preceding evening should be checked. If there has been a voiding after 11 p.m., the repeated finding of sugar in the urine before breakfast is an indication for increasing the protamine zinc insulin. If there has been no voiding since earlier in the evening, judgment concerning the adequacy of the dose of protamine zinc insulin should await the analysis of a second voiding before breakfast. If the second specimen obtained — by having the patient drink one or two glassfuls of water — during the next three quarters of an hour contains sugar, the dose of protamine zinc insulin may be increased by 2 to 4 units.

The appearance of too much sugar in the urine due to an infection or to some other temporary disturbance is best controlled by a small amount of plain insulin before supper. An adequate supplementary dose of this type is 4 to 8 units, depending on the amount of the routine dose administered before breakfast.

In the treatment of coma, the clinician now utilizes the advantages incident to the immediate use of protamine zinc insulin and plain insulin, and of enough parenteral sodium lactate in the initial parenteral-fluid therapy to correct the hyperventilation, and so put the patient at rest in the first hour of therapy and pave the way to recovery within six to eight hours. The appropriate parenteral-fluid therapy can be estimated by the clinical appraisement of the degree of dehydration and acidosis, and can be administered without elaborate physiological calculations or chemical analysis.[39]

Thus has the physician advanced the art of effective and economical medical care with the tools that have been made available. He need not be ashamed of his accomplishment, but he cannot be satisfied with it. He still ponders the old question: Should it be a high-carbohydrate or a low-carbohydrate diet? Eagerly, he awaits the answer from such work as that of Best and his co-workers,[12] which thus far not only casts doubt on the validity of the widely accepted but unproved theory that the high-carbohydrate regimes of today favor the insulinogenic capacity of the pancreas, but also suggests that the glycosuria and hyperglycemia of such regimes inhibit the recuperative power of the cells of the pancreatic islets. Often he worries: will our present degree of control of diabetic patients, which prevents transient ketosis, hypercholesterolemia, enlargement of the liver and appreciable glycosuria, prevent in the future such diabetic cardiovascular diseases as have occurred in the past? And while he wonders, he scans with hope the newer knowledge of the pituitary[6] and adrenal[9] hormones and of the cellular enzymes,[7] for there new means of therapy may lie untouched.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Ante-mortem and Post-mortem Records as Used in Weekly Clinicopathological Exercises

founded by richard c. cabot

Tracy B. Mallory, M.D., *Editor*

CASE 26481

Presentation of Case

A seventy-year-old housewife entered the hospital complaining of pain in the legs and back.

Eighteen months before admission, after a day of strenuous housecleaning, the patient developed a moderately sharp pain in the left hip that radiated down the posterior aspect of the leg to the heel. This pain remained constant for the next few days, and although troublesome, it did not interfere with work or sleep. Then it became intermittent, recurring every week for the next seven months and finally disappearing within a few weeks thereafter. She remained symptom free until six months before admission, when the pain reappeared in a less severe form; it was aggravated by activity but completely relieved by rest, and was accompanied by a dull ache in the lower back. Two weeks later the patient noticed a similar, radiating pain in the right hip that was constant and alternately dull and sharp. During the next few months the pain increased, but she continued to work. One night, five weeks before admission, while getting into bed she heard a "click" in the lower spine, followed by a painful, involuntary muscle spasm involving first the right then both legs, with the result that they were flexed on the abdomen. The spasm relented and recurred many times during the night, and she suffered from pain in the hips, groin, buttocks and legs. The attacks of muscle spasm decreased in number, and within a few days she was able to get about the house, and, indeed, preferred to sit upright, for lying flat caused unbearable paroxysms of pain. During this time the legs felt "numb and prickly." Two weeks before admission, when the patient entered another hospital, muscle spasm still occurred several times a day, lasted a few minutes and was followed by soreness of the leg muscles and lower abdomen. The attacks were precipitated by turning in bed, and the patient consequently remained on her back, with the result that a sacral bedsore developed. There were no accompanying constitutional symptoms, but she had lost 15 pounds in the few months prior to entry.

The patient had suffered from scarlatina at nine years of age and had had frequent sore throats in her youth and intermittent psoriasis since childhood. At twenty-one she spent three months in bed because of "bronchitis" characterized by a low fever, cough and blood-streaked sputum. Her physician said she had "a spot on her left lung." There had been no recurrence of this illness.

Physical examination showed a well-developed and well-nourished woman in no acute distress. There was a psoriatic desquamation over the elbows and wrists. Each sclera showed an arcus senilis, and the fundi minimal arteriolarsclerosis. Examination of the heart and lungs was negative; the blood pressure was 160 systolic and 90 diastolic. Examination of the abdomen was negative, although one examiner believed that there was a vague nontender mass in the right upper quadrant. A 7-cm. ulcer with a gray, oozing base was present over the sacrum. Neurological examination was negative except that the left knee jerk was more active than the right. Rectal examination was negative; vaginal examination revealed a marital introitus and a smooth, soft, atrophic cervix. The fundus could not be felt, and the vaginal vaults were clear.

The temperature was 99°F., the pulse 103, and the respirations 20.

Examination of the urine showed a + test for albumin, and a negative test for Bence–Jones protein on five occasions. Examination of the blood showed a red-cell count of 5,280,000 with a hemoglobin of 14.1 gm. (photoelectric-cell technic), and a white-cell count of 9900 with 72 per cent polymorphonuclears. No plasma cells were seen. The sedimentation rate was 39 mm. in one hour. The nonprotein nitrogen of the blood was 23 mg. per 100 cc., and the serum protein 7.4 gm. The serum calcium was 10.9 mg. per 100 cc., the phosphorus 4.3 mg., and the phosphatase 6.8 units. A blood Hinton test was negative. A tuberculin test was negative in a dilution of 1:10,000, but positive in 1:1000, the area of induration and erythema measuring 1.5 cm. in diameter. Agglutination tests were negative for *Eberthella typhi, Salmonella paratyphi, S. schottmülleri* and *Brucella abortus*. Examination of the stools was negative.

X-ray examination of the spine showed obliteration of the joint between the twelfth dorsal and first lumbar vertebrae, and extensive destruction of the inferior margin of the body of the twelfth dorsal and of the superior portion of the body of the first lumbar vertebra. The bones of the vertebrae were unusually dense, but there was very little new-bone formation about their margins. There was a paravertebral mass on the left side, extending from the level of the ninth

dorsal to that of the second lumbar vertebra, and a similar slightly lower mass on the right. Roentgenograms of the other vertebrae, the skull and chest were negative. A comparison of these films with those taken elsewhere showed no appreciable advance in the destructive process.

An intravenous pyelogram taken with a portable machine showed prompt excretion of the dye on both sides. Both renal pelves and calyxes were moderately dilated, and there was a pressure defect in the pelvis and lower calyxes on the left, produced by the paravertebral mass. In films taken approximately two months later, the medial portion of both kidney pelves showed a pressure defect. In some of the films there was also a suggestion of mass in the midpelvis.

The patient was placed in a Bradford frame, but continued to have attacks of muscle spasm and pain in the legs. The sacral ulcer gradually increased in size. Three weeks after admission she had an attack of nausea, vomiting and diarrhea that subsided within three days. At that time the knee and ankle jerks were equal, but hyperactive; the plantar reflexes were normal. A sternal puncture two months after admission showed a normal bone marrow. Nine weeks after admission, an aspiration and punch biopsy of the body of the twelfth dorsal vertebra was performed.

Differential Diagnosis

Dr. James R. Lingley: The x-ray films reveal a very definite process involving the twelfth dorsal and first lumbar vertebrae, with extensive bone destruction about the margins of the adjacent vertebral bodies, complete destruction of the intervertebral disk and marked increase in the density of both vertebral bodies. Some of the films show a suggestion of a soft-tissue mass above the margins of the vertebrae, and possibly a little calcification in the mass. The other bones appear normal except for some decalcification.

Dr. Charles L. Short: The abstract says that there were two paravertebral masses. Are they quite definite?

Dr. Lingley: The one on the right is quite definite — the psoas muscle definitely bulges. I am not so sure about the one on the other side.

Dr. Short: Other films are said to show pressure defects, apparently from the paravertebral masses.

Dr. Lingley: There is a pressure defect in the left renal pelvis. That confirms the impression of a mass on the left. Although the pelvis is not well visualized, there seems to be a mass on the right. Hence, there are bilateral masses.

Dr. Short: The x-ray findings will probably give us the most valuable information for a diagnosis of this case. I should therefore like to summarize these findings, and Dr. Lingley will correct me if I am wrong. In the first place, there is a destructive spinal lesion that started, perhaps, in the intervertebral disk, but that may have started in one or the other of the two vertebrae. The paravertebral masses extend down, obstructing the kidney pelves. The other x-ray films show no evidence of a primary lesion or of a primary infectious focus, and also no evidence of generalized bone disease. Apparently the only lesion was in the spine. I think the patient's history can also be explained on the basis of the x-ray findings. There was pain in the legs from pressure on or irritation of the nerve trunks. The remission of four months in the course of the illness might have resulted from an inflammatory rather than a neoplastic lesion, although pressure effects from neoplasms may disappear temporarily. The flexion spasm of the legs can be explained by the involvement of the psoas muscles with the masses visible in the x-ray films. One wonders on reading the history whether the patient was in danger of developing paraplegia, but examination in the hospital showed only suggestive evidence of pressure on the motor tracts — that is, the unequal knee jerks and, later, the increased knee jerks. A lumbar puncture was not made, probably wisely. There might have been danger of infection, because of the presence of the bedsore, or even of going through one of the paravertebral lesions. There is no mention of the examination of the spine in the physical examination. I suppose that it was not believed to be helpful, but we should like to know whether there were any local findings.

Dr. Tracy B. Mallory: There is no note about the spine in the record of the physical examination, or even in the notes made after her transfer to the Orthopedic Service.

Dr. Short: I assume that there was some rigidity in the back and some tenderness. I do not believe that one can bring the psoriasis into the differential diagnosis. Certainly this is not rheumatoid arthritis. The bronchitis that the patient had fifty years ago is of some interest. This evidently was before the days of x-rays, and we do not know whether it was a tuberculous or a nontuberculous process in the chest.

The laboratory work is helpful largely in ruling out possibilities. Apparently the people taking care of this patient thought first of a neoplastic process, and it is evident that they considered multiple myeloma a leading possibility. There was no Bence-Jones protein in the urine.

The serum protein was high, but probably within normal limits. There were no plasma cells in the blood smears, and no evidence of multiple lesions in the other bones. Finally a biopsy of the sternum was done, with negative findings. These things do not rule out multiple myeloma, of course, but taken together they present very strong evidence against it. There was no evidence of a primary focus, if the lesion represented a metastatic process.

If we do call this a neoplasm, it is difficult to account for the two paravertebral masses. Of course a tumor could spread in this way, but the most likely form of neoplastic process in this case, if there is one, is lymphoma, which could give a lesion resembling this one. However, we have no positive evidence. There were no enlarged lymph nodes, the spleen was not palpable, and the patient had gone on eighteen months without any sign of lymphoma elsewhere in the body. This does not rule out the diagnosis, but makes it unlikely.

I favor an infection, rather than a neoplasm, as explaining this picture — that is, a primary infection starting in either the vertebrae or the intervertebral disk and spreading so as to cause irritation of the psoas muscles and some obstruction to the outflow of the kidneys.

Another possibility is a neoplasm with secondary infection. I do not see how we can decide that point. We can hardly say that this is an acute osteomyelitis, because constitutional symptoms and so forth are lacking. I do not believe that even a more chronic infection like undulant fever could cause this picture for so long a time without the patient's having had some evidence of a febrile reaction, although a spinal lesion of this sort with secondary abscess formation is not uncommon in undulant fever.

There are other, more chronic, types of infection such as syphilis, and we have no way of completely ruling them out. But we do have a negative history and a negative blood Hinton test, which are unusual for a syphilitic lesion. A chronic osteomyelitis of the spine might give a picture like this, but one would expect a constitutional reaction at one time or another.

You will probably see that I am leading up to a diagnosis of tuberculosis. The chronicity, the lack of constitutional reaction, the location of the process and the secondary abscess formation, if these are abscesses, would make a diagnosis of tuberculosis quite likely if this patient were a child. We should consider that first in diagnosis. I do not know why there was more bone reaction than we usually see in tuberculosis. Is that correct?

Dr. Lingley: There is more than you would expect, although there is usually some reaction.

Dr. Short: There is no such bone production as one sees with a pyogenic process. It would be a help to bring in, as the primary infection, the illness that the patient had at twenty-one years of age; but we have no way of doing that. Tuberculosis does occur at this age, and may involve the spine, but of course it is quite rare, although childhood forms such as tuberculosis of the lymph nodes and tuberculous peritonitis occur in old people. That is the diagnosis that I finally arrived at, but I should agree with those who took care of the patient that a biopsy would be very essential to getting the final answer.

A Physician: Was there a chest film?

Dr. Lingley: Yes; it was negative.

Dr. Joseph S. Barr: I agree that tuberculosis is the most likely diagnosis in this case. The x-ray films show such an extensive lesion that the patient must have had it for a considerable length of time. The adult intervertebral disk has no blood supply, and consequently there cannot be a blood-borne infection in the disk. So far as we know pathologically, these lesions begin very close to the disk and destroy it by direct extension, secondarily invading the vertebral bodies on either side.

Dr. Bernard M. Jacobson: I saw this patient about a month and a half or two months after she came in, and my studies furnished fairly conclusive evidence against multiple myeloma. The Orthopedic Service thought that metastatic carcinoma was the best bet. She was an old lady who wanted very much to go home, and just as she was about to be discharged, the service, after a good deal of urging, decided to do a punch biopsy.

Clinical Diagnosis

Metastatic carcinoma?

Dr. Short's Diagnosis

Tuberculosis of spine.

Anatomical Diagnosis

Tuberculosis of spine.

Pathological Discussion

Dr. Mallory: The punch biopsy was successful in this case. Several fragments were obtained that showed tubercles in various stages, thus substantiating Dr. Short's diagnosis.

CASE 26482

Presentation of Case

A thirty-six-year-old Italian cook entered the hospital after vomiting large quantities of blood.

Two years before admission, the patient began to suffer from epigastric pain, coming on one hour after meals, relieved by food or soda and accompanied by belching and a feeling of fullness. His physician made a diagnosis of peptic ulcer and prescribed a dietary regime and alkalies. The patient improved under this treatment, and within three months the pain disappeared. Eight months before admission, the epigastric pain returned, and one month later he vomited "about two quarts" of bright-red blood, after which the stools were tarry for a week. A gastrointestinal examination at this time showed an ulcer half way down the lesser curvature of the stomach. The patient was again placed on an ulcer regime and was able to return to work in one month. However, he gradually abandoned the diet and started to smoke and drink a great deal, with the result that the pain returned three months before admission. He ignored the symptoms until one month before admission, when the stools became tarry for a week. The patient then returned to his physician; another gastrointestinal examination showed little change in the ulcer, which was described as having a 1.5-cm. base. Ten days before admission he vomited blood, felt weak and exhausted and remained in bed, but still did not follow the diet faithfully. On the morning of admission, he suddenly felt weak and nauseated, and shortly afterward had a large hematemesis. Two hours later he vomited bright-red blood three times within forty-five minutes.

The patient had had indolent leg ulcers for some years. The family history was irrelevant.

Physical examination showed the patient to be well-developed, but poorly nourished and extremely pale. The skin was dry and showed evidence of recent loss of weight; the extremities were cold and clammy. Examination of the lungs was negative. The heart was not enlarged or irregular, but the sounds were weak and rapid, with a ticktack quality. The pulse was barely perceptible; the blood pressure was 56 systolic, 35 diastolic. The abdomen was soft and well relaxed, with some tenderness low in the epigastrium. The patient had received ⅙ gr. of morphine immediately before entry. The legs showed varices, with eczema, pigmentation and ulceration. Examination of the nervous system was negative.

The temperature was 98°F., the pulse 105, and the respirations 25.

Examination of the urine was negative. The blood showed a red-cell count of 1,950,000 with a hemoglobin of 49 per cent, and a white-cell count of 12,350. The nonprotein nitrogen of the blood serum was 25 mg. per 100 cc., the prothrombin time 16 seconds, and the cell volume 22.9 per cent. Four stool examinations were guaiac positive.

The patient was placed on a Sippy regime and was given five 500-cc. transfusions within the next six days. He improved satisfactorily, and the red-cell count rose to 3,360,000, the hemoglobin to 60 per cent. On the seventh hospital day he vomited 500 cc. of bright-red blood, and two days later an equal quantity, with a consequent drop in the red-cell count to 1,330,000 with a hemoglobin of 25 per cent. Once again the patient was guided up the Sippy ladder, and was given daily blood transfusions and intravenous fluid with added vitamins. On the eighteenth hospital day he had a transient but sudden acute attack of abdominal pain and passed a large quantity of gas by mouth and rectum. The following day three hematemeses occurred, with an approximate total loss of 800 cc. of blood. On the twentieth hospital day fluoroscopic examination showed a large crater on the lesser curvature of the stomach, approximately 4 cm. below the cardia, with marked surrounding induration. The stomach was filled with material consistent with blood, milk or tumor. On the same day an operation was performed.

Differential Diagnosis

Dr. Edward Hamlin, Jr.: This appears to be a definite case of gastric ulcer with recurring massive hemorrhages. Presumably when the patient entered the hospital he was placed on the Medical Service and was given a transfusion; when it was found that despite excellent medical care he continued to have hemorrhages, a surgical consultant was called, who agreed that the patient's best chance lay in surgery. The fluoroscopic examination was undertaken the day of operation to determine the exact site of the lesion and to exclude esophageal varices.

Dr. Aubrey O. Hampton: This patient was not examined in the upright position because of his condition. These films were taken as he lay on the table. There is the crater of the ulcer—an apparently huge lesion on the lesser curvature. It is magnified because of the position in which it was taken and is probably only about 2.5 cm. in diameter. The mucosal folds 1 cm. away are normal; those next to it are invisible, due to edema

and swelling. The conclusion of the X-ray Department was that the lesion was benign but unusually large.

DR. HAMLIN: The only other diagnosis that we need consider carefully is carcinoma. There are other possibilities, but it would be an unjustifiable waste of time to discuss them. From a statistical point of view everything seems to be in favor of benign ulcer. The patient is in the proper age group for an ulcer. Carcinoma of the stomach in that position is said to occur in only 25 per cent of the cases, and massive hemorrhages, such as this patient had, are considered somewhat unusual. The early history of periodic pain relieved by food and soda and the long remission following dietary treatment are quite typical of ulcer. But during the last few months, even after entry to the hospital and thoroughly controlled medical care, the patient did not cease to bleed and the ulcer crater appears to have increased in size. Finally the x-ray report notes an area of induration about the crater.

The surgeon's real responsibility in such a case is not so much to make an accurate preoperative diagnosis as to consider the possibility of carcinoma so that he will be able to deal with it if he finds the slightest confirmatory evidence on exploration. With the increasing size of the lesion and the surrounding area of induration, I should say that the surgeon made a preoperative diagnosis of carcinoma of the stomach and that was what he found.

DR. TRACY B. MALLORY: Are there any other suggestions?

DR. RICHARD H. SWEET: Would you consider lymphoma? I am not proposing that as a diagnosis, but I have the impression that ulcerative lymphomatous tumors are apt to produce massive hemorrhage in the gastrointestinal tract.

DR. HAMLIN: Lymphomas and sarcomas both are supposed to.

DR. F. DENNETTE ADAMS: Does not the fact that he not only failed to improve but grew worse under presumably excellent medical treatment seem very good evidence that there was more than ulcer?

DR. HAMPTON: I should like to add that the X-ray Department cannot be expected to make the differential diagnosis in such a lesion.

DR. WILLIAM B. BREED: Of course if you make a diagnosis of cancer you are going against the figures a good deal. This is a fairly straightforward case, and I do not believe there is enough evidence to make one put cancer first.

DR. HAMLIN: My argument was based on the fact that with a definite diagnosis of ulcer one would do a somewhat different operation than if one believed there was a possibility of cancer, and in this particular case the latter is so prominent that, at the first corroborative sign, a radical resection of the omentum should be done.

DR. BREED: It is often difficult for the surgeon to make a diagnosis of cancer even on inspection and palpation.

DR. REGINALD H. SMITHWICK: This was an unusual and interesting case. Those of us who saw the patient thought that he probably had a benign ulcer, but we realized, of course, that it was unusual for a man of thirty-six years of age to bleed as excessively as he did after three weeks of medical treatment in the hospital. Of course his general condition was desperate before operation, and our chief concern was to decide what was the best procedure, rather than to speculate as to the true nature of the lesion. Certainly, from the medical course of the last three weeks, there seemed to be little possibility that the patient would survive on a continued Sippy regime. For that reason, we operated, realizing that his chances of surviving operation were also very slim. We thought that perhaps a reasonable explanation for the bleeding was the location of the ulcer, which was comparable with that of the persistent bleeding ulcers that one sees in the duodenum. In this case it was located exactly where the left gastric artery goes into the stomach, and it seemed possible that a large branch of the artery was in the base of the ulcer. One would therefore not have to assume cancer to explain the bleeding. When we operated, it was very obvious on exploration and palpation of this lesion that it was carcinoma. There were some large nodes that ran up along the left gastric vessels, and the ulcer did involve branches of the left gastric artery; furthermore, when we had freed up the stomach and omentum, we could palpate a small subserous nodule in the wall of the stomach about a centimeter or two above the upper border of the ulcer, which was further evidence that the lesion was malignant. The later finding necessitated taking out practically the whole stomach; this was a little more than we wished to do in a patient in this condition, but we could handle the situation in no other way.

CLINICAL DIAGNOSIS

Bleeding peptic ulcer.

Dr. Hamlin's Diagnosis

Carcinoma of stomach.

Anatomical Diagnosis

Carcinoma of stomach.

Pathological Discussion

Dr. Mallory: The specimen that was received in the laboratory showed a large area of ulceration, in the base of which several small eroded arteries were evident. The borders were hard and cartilaginous in consistence, and it was quite obvious that the ulcer was malignant. Microscopic examination showed a fairly well-differentiated adenocarcinoma. The patient survived resection, and was sent home in fair condition.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
The New Hampshire Medical Society
The Vermont State Medical Society

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

CHRISTMAS SEAL CAMPAIGN

The National Tuberculosis Association and its numerous affiliated associations throughout the country have no support but the contributions that once a year are given — dollar by dollar, two by two, five by five — to enable this vast organization to continue its campaign for the protection of health, happiness and life.

The money contributed has helped the organized attack that has cut the death rate of tuberculosis to one quarter of what it was in 1907, when the Seals were first sold; it has financed one of the greatest health-education programs ever carried on in this country. Tuberculosis must be defeated by educating the people, because science has as yet found no vaccine to prevent the disease, no drug for its cure.

Education, paid for by the Christmas Seal dollars, is the most effective vaccine. The money has also played a part in establishing clinics and in developing new methods of diagnosis; it has shown that early tuberculosis can be diagnosed, with the result that the hopelessness once associated with the disease has been largely dispelled.

In spite of these advances, however, the final victory is yet to be won. Tuberculosis is still the chief cause of mortality among people between fifteen and forty-five years of age. And it still kills one person every eight minutes.

The campaign must go on to ultimate success, which is possible within the next few decades. The advances already made in curing and controlling the disease emphasize the responsibility of the public for next year and the years to come.

Without financial support, the fight cannot continue. A few dollars a year at Christmas time are little enough to pay for the protection of the life and health of a nation.

GRENFELL'S MISSION

The death of Sir Wilfred Thomason Grenfell brings attention to a dramatic achievement in the world of medicine. Those who have caught the spark of his enthusiasm and know his work intimately will carry on in confidence that only the first chapter is ended, and that what has been built will remain a permanent contribution to civilization in the North.

As a young physician, Grenfell saw the need of medical care for the scattered fishing population of the remote coasts of northern Newfoundland and Labrador. Convinced that his services would mean more to this pioneer fringe than to the dwellers in the city, where doctors are many, he went. And, in the people of the North, he saw self-reliance, simple and rugged virtues, generous hospitality and similar qualities rarely seen where life is easier. Others have practiced medicine in lonely places, but few have inspired such a host of

worshiping followers to build a great medical service.

Grenfell's personal qualities were extraordinary. The magnetism with which he drew young and old to his standard was almost without parallel. Many persons are kind-hearted, many are strenuous workers, many are abler executives and administrators than he; but it took something greater than any or all of these to make him what he was. A stalwart Briton, he had none of the stolid Anglo-Saxon in his make-up; his quick wit, his facile imagination, his keen vision — far more artistic than logical — all these marked him rather as Celtic in his traits. Combined in him were intensely warm humanity, the fire of enthusiasm and a spiritual philosophy of life, with a spark of true genius running through it all, which made him an altogether unique figure. He was deeply religious but without a trace of bigotry or cant, and the very practical character of religious devotion that he brought to bear on his medical work was the keynote of his life.

He told of finding a widow with starving children on the coast near where game abounded, and of giving her a shotgun and shells with which to provide meat for her family. "I thought that was the way to preach the Gospel to her," he said simply. He would give seed to those who would plant it and raise vegetables, and prizes for the best gardens. But he discouraged the giving of dole without responsibility, and compared this to food without vitamins, leading to paralysis

If he was sometimes inconsistent and gave to the needy from his "discretionary fund," even to the point of pauperizing the recipients, it should be recalled that it is difficult for anyone to be "hard-boiled" and strictly businesslike when encountering those in dire want, especially for one so brimming with kindness and compassion as he was. It is easy to forgive such a fault in one of his impulsive nature. But if the mission he created is to build a better civilization in the North, his wise doctrine of encouraging self-help and self-reliance must prevail.

OBITUARY

FRANCIS EDWARD PORTER

1844 – 1940

Dr. Francis Porter passed away on October 11, after a long debilitating illness. He was born in Scituate on August 28, 1844. His early education was received there, followed by four years at Wesleyan University, from which he graduated in 1869. He graduated from Harvard Medical School in 1872. The following year he interned at the Massachusetts General Hospital, and the next two years were devoted to postgraduate study at Vienna and other European medical centers. One of his most cherished recollections was his personal association with Lister in Edinburgh and with Pasteur in Paris. At this time these two scientists were just beginning their wonderful contributions to the scientific world.

In 1875 he opened an office for the practice of medicine in Auburndale, where he worked untiringly until 1920, when failing health and partial loss of sight necessitated discontinuance of professional activities.

Dr. Porter was a member of the original staff of the Newton Hospital, where he served as physician, later as surgeon, and from 1910 to 1920 as consulting surgeon. He was a trustee of the hospital from 1910 to 1920. In 1923 he was honored by having the addition to Dennison Ward named Porter Ward.

Dr. Porter gave gladly and freely of his time and strength for the care of the sick and afflicted. By example and advice he assisted many young men as they began the practice of medicine. His thorough training, academic and professional, supplemented by postgraduate study and coupled with years of experience, made him one of the outstanding members of the profession.

The medical profession of Newton mourns the passing of one of its most highly esteemed members, this grand old man of the "old school."

H. F. K.
L. H. J.
F. R. C.

MEDICAL EPONYM

Fick Principle

Professor Adolf Fick (1829–1901), of Würzburg, discussed "Ueber die Messung des Blutquantums in den Herzventrikeln [The Measurement of the Amount of Blood in the Ventricles]" on July 9,

1870, before the Physicomedical Society of Würzburg. An abstract of his discussion appears in the *Verhandlungen der physikalisch-medizinischen Gesellschaft in Würzburg: Sitzungsberichte für 1870* (2 [Neue Folge]: xvi, 1872). A portion of the translation follows:

> The amount of oxygen taken from the air by an animal during a given time is measured, as well as the amount of carbon dioxide given off. During the experimental period, samples of arterial and of venous blood are also taken. The oxygen content and carbon dioxide content are measured in both. The difference between the two oxygen measurements reveals how much oxygen each cubic centimeter of blood has taken up in its passage through the lungs, and thus we know the total amount of oxygen absorbed during a definite period of time. Consequently the number of cubic centimeters of blood that passed through the lungs during this time may be reckoned, or if we divide by the number of heart beats during this period of time, we may determine how many cubic centimeters of blood were put out with each cardiac systole.

R. W. B.

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Boston

PREGNANCY COMPLICATED BY TOXEMIA AND DIABETIC COMA

Mrs. W., whose previous history and pregnancy were recorded in the November 21 issue of the *Journal,* was seen on September 23, 1937, in the seventeenth week of her second pregnancy. The last period began on May 16, making the expected date of confinement February 23, 1938.

At the time of her visit the diabetes was well controlled. The weight at the start of the pregnancy was 155 pounds, and she had gained 12 pounds. The blood pressure was 128 systolic, 80 diastolic. The fundus was enlarged to a size consistent with her dates.

The patient was followed very closely by her obstetrician and a specialist in diabetes. At the beginning of the seventh month of pregnancy, signs of toxemia were present, since the Smith–Smith† test showed that the prolan had risen to 200 rat units per 100 cc. of blood. Treatment, in the form of Progynon on the average of 150,000 to 300,000 international units and Proluton on the average of 10 to 20 mg. daily, was immediately instituted. This dosage varied from day to day.

On December 17 the blood pressure rose to 130 systolic, and there was some edema; examination of the urine was negative, however. The patient was sent to the hospital, where she did very well, losing 3 pounds in four days. On December 22 the urine contained a definite trace of albumin, but the weight had gone down another 3 pounds. On December 23 the patient was in diabetic coma. The blood carbon dioxide content had dropped to 19 vol. per cent. The blood pressure was 120 systolic, and there was a very slight trace of albumin in the urine. The fetal heart was audible. At that time she was approximately thirty-two weeks pregnant. After the patient recovered from the coma, the diabetes remained stabilized, and the blood pressure remained at a normal level.

On January 10, 1938, when the patient was about thirty-five weeks pregnant, delivery was considered necessary because the fetal heart was heard, because the patient had gained 1 pound in twenty-four hours and because the blood pressure showed extreme vacillation — 120 to 150 systolic. A cesarean section was done because the cervix was not favorable for induction and because the baby was alive. The baby weighed 7 pounds, 11 ounces, survived and is well today. The mother's convalescence was uneventful.

Comment. This case illustrates the advance in the last two or three years in the treatment of diabetic patients with toxemia of pregnancy. Today the prolan in all diabetic patients is estimated early in pregnancy, usually from the twentieth to the thirty-second week, by the Smith–Smith method. This is very important, because at least 25 per cent of all diabetic patients show toxemia. The test is repeated during pregnancy, and if the prolan is high, — 200 rat units per 100 cc. of blood, — Progynon and Proluton are given, sometimes in very large doses, to reduce this level. In this case the establishment of the diagnosis of probable toxemia resulted in a living child in a mother who two years previously had lost a fetus in utero from diabetic toxemia. That this new treatment is not uniformly successful, however, will be illustrated in a case to be published next week.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

†Smith, G. V., and Smith, O. W.: Estrogen and progestin metabolism in pregnant women: with special reference to pre-eclamptic toxemia and effect of hormone administration. *Am. J. Obst. & Gynec.* 39:405-422, 1940.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning December 2:

BARNSTABLE

Sunday, December 8, at 4:00 p.m., at the Cape Cod Hospital, Hyannis. Management of Abdominal Distention. Instructor: Henry H. Faxon. Donald E. Higgins, *Chairman.*

BRISTOL NORTH

Thursday, December 5, at 4:00 p.m., at the Morton Hospital, Taunton. Dermatitis and Eczema. Instructor: Francis P. McCarthy. Lester E. Butler, *Chairman.*

BRISTOL SOUTH (New Bedford Section)

Friday, December 6, at 4:00 p. m., at St. Luke's Hospital, New Bedford. Technic and Treatment of Primary, Secondary and Tertiary Syphilis. Instructor: William P. Boardman. Robert H. Goodwin, *Chairman.*

ESSEX NORTH

Friday, December 6, at 4:30 p.m., at the Clover Hill Hospital, Lawrence. Chemotherapy in the Treatment of Gonococcal Infection. Instructor: P. N. Papas. John Parr, *Chairman.*

ESSEX SOUTH

Tuesday, December 3, at 4:00 p.m., in the Conference Room, Salem Hospital, Salem. Management of Abdominal Distention. Instructor: Hollis L. Albright. J. Robert Shaughnessy, *Chairman.*

MIDDLESEX NORTH

Friday, December 6, at 5:00 p.m., at St. John's Hospital, Lowell. Pediatric Case Discussions. Instructor: R. Cannon Eley. William S. Lawler, *Chairman.*

PLYMOUTH

Tuesday, December 3, at 4:30 p.m., in the Nurses' Home of the Brockton Hospital, Brockton. Recent Advances in Medical Therapeutics. Instructor: Charles A. Janeway. Walter H. Pulsifer, *Chairman.*

DEATHS

O'ROURKE — EDWARD J. O'ROURKE, M.D., of Cambridge, died November 20. He was in his fifty-fifth year.

Born in Cambridge, he attended Cambridge High and Latin School and received his degree from Tufts College Medical School in 1909. He was a fellow of the Massachusetts Medical Society and the American Medical Association and held memberships in the Cambridge Medical Improvement Association and the Medical Library Association. He was on the staff of the Cambridge City Hospital.

His widow, a daughter and three sons survive him.

ROGERS — FRANK A. ROGERS, M.D., of Roxbury, died November 15. He was in his eighty-sixth year.

Born in West Newfield, Maine, he received his degree from the Bowdoin Medical School in 1876. For several years he practiced in Everett, where he served as chief health officer and school physician. Dr. Rogers was a retired member of the Massachusetts Medical Society and the American Medical Association.

His widow, a sister, two sons and two daughters survive him.

WALKER — MELVIN H. WALKER, JR., M.D., of Pittsfield, died November 21. He was in his fifty-fifth year.

Born in Westboro, he attended Yale University and received his degree from Harvard Medical School in 1915. He was a member of the Pittsfield Board of Health for seven years and a member of the surgical staffs of the House of Mercy and St. Luke's hospitals, Pittsfield.

Dr. Walker was a fellow of the Massachusetts Medical Society, the American Medical Association and the American College of Surgeons.

His widow and two daughters survive him.

MISCELLANY

THE BULLETIN OF WAR MEDICINE

Developments of the war during the last year have made it very difficult to obtain medical journals from Europe. In order that information of the valuable work being done should be available to the medical profession, the British Medical Research Council has arranged for the publication of the *Bulletin of War Medicine,* which contains abstracts and summaries of all relevant modern literature on the subjects considered.

Medical experiences arising from the present war have not as yet been largely reported, but papers are appearing in this literature in steadily increasing numbers, and it is proposed, if circumstances permit, to issue the *Bulletin* every two months.

The articles in the first number, which is dated September, 1940, are arranged as follows:

WOUNDS AND INJURIES	
General Considerations	5 abstracts
Shock	5 abstracts
Surgery of Special Regions	20 abstracts
Plastic Surgery	6 abstracts
ANESTHESIA	3 abstracts
BLOOD TRANSFUSION	11 abstracts
X-RAYS AND RADIOACTIVE SUBSTANCES	5 abstracts
DISEASES	
General Diseases	1 abstract
Diseases of Special Systems	6 abstracts
Psychological Medicine	5 abstracts
Venereal Diseases	4 abstracts
WAR GASES AND EXPLOSIVES	6 abstracts
PHARMACOLOGY AND GENERAL THERAPEUTIC MEASURES	2 abstracts
NAVAL MEDICINE	4 abstracts
AVIATION MEDICINE	12 abstracts
INDUSTRIAL MEDICINE	3 abstracts
FOOD AND DRINK	5 abstracts
GENERAL SANITATION	1 abstract
CIVIL EVACUATION	5 abstracts

The first number consists of 62 pages, and the price is 75 cents. It may be ordered through the British Library of Information, 50 Rockefeller Plaza, New York City.

NOTE

Six appointments to the teaching and research staff of the Harvard Medical School were recently announced by the University as follows: (effective September 1, 1940) Robert G. Snow, M.D. Harvard '35, assistant in laryngology, courses for graduates; Albert E. Sloane, M.D. Tufts '33, assistant in ophthalmology, courses for gradu-

ates: (effective November 1, 1940) Gerald F. Houser, M.D. University of Toronto '28, instructor in preventive medicine; William H. Sweet, M.D., Harvard '36, assistant in neurosurgery; Everett I. Evans, M.D. '37, University of Chicago, research fellow in surgery; Ernest M. Morris, M.P.H. Harvard '38, instructor in public-health practice.

REPORT OF MEETING

NEW ENGLAND SOCIETY OF PSYCHIATRY

The regular fall meeting of the New England Society of Psychiatry was held at the Northampton State Hospital on Thursday, October 24. Approximately one hundred and fifty members attended.

The morning was given over to inspection of the hospital. Luncheon was served at 1 p.m. in the hospital cafeteria. Dr. Roy D. Halloran, Superintendent of the Metropolitan State Hospital, Waltham, Massachusetts, presided at the afternoon meeting, at which the following were elected to membership: Bessie F. Brown, Wrentham; Richard C. Cooke, Waltham; Emerick Friedman, Norwich, Connecticut; Patrick J. Meehan, Tewksbury; Margaret R. Simpson, Foxboro. Memorial resolutions were read regarding the deaths of the following: G. Alder Blumer, Providence, Rhode Island; Martin W. Peck, Boston; Mary Theresa Muldoon, Waverley.

Dr. D. Ewen Cameron, professor of neurology and psychiatry at Albany Medical School, Albany, New York, presented a very interesting paper entitled, "The Influence of the Times on the Teaching of Psychiatry." He emphasized the need for a reorientation of concepts made necessary by changing conditions of community life and by modern work on causative factors in abnormal mental states.

BARDWELL H. FLOWER, M.D., *Secretary.*

NOTICES

ANNOUNCEMENT

CHARLES A. ROBINSON, M.D., announces the removal of his office from 942 Broadway, South Boston, to 270 Commonwealth Avenue, Boston.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Thiede, formerly concertmaster of the Cleveland Symphony Orchestra, every Thursday at 8:30 p.m. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will take place on Tuesday, December 10, in the amphitheater of the Peter Bent Brigham Hospital at 8:15 p.m.

PROGRAM

Presentation of cases.

The Relation of Forensic Medicine to Public Health. Dr. Thomas A. Gonzales, chief medical examiner, New York City.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM, DECEMBER–JANUARY

Tuesday, December 3 — Case Study of Adrenal Deficiency in an Infant. Drs. F. C. McDonald and Nicholas Werthessen.

Wednesday, December 4 — Hospital case presentation. Dr. S. J. Thannhauser.

Thursday, December 5 — Vascular Disease as Seen in the Ocular Fundi. Dr. Benjamin Sachs.

Friday, December 6 — Some Aspects of the Aging Heart. Dr. H. B. Sprague.

Saturday, December 7 — Hospital case presentation. Dr. S. J. Thannhauser.

Tuesday, December 10 — Some Geographical Differences in Surgical Diseases. Dr. Rudolf Nissen.

Wednesday, December 11 — Hospital case presentation. Dr. S. J. Thannhauser.

Thursday, December 12 — Pathogenesis of the So-Called "Metasyphilis" (General Paresis, Tabes). Dr. Alfred Hauptmann.

Friday, December 13 — Clinicopathological conference. Dr. W. B. Castle.

Saturday, December 14 — Hospital case presentation. Dr. S. J. Thannhauser.

Tuesday, December 17 — The Clinical Significance of the Hypothalamus. Dr. Kurt Goldstein.

Wednesday, December 18 — Hospital case presentation. Dr. S. J. Thannhauser.

Thursday, December 19 — Title to be announced.

Friday, December 20 — The Banti Syndrome. Dr. L. K. Diamond.

Saturday, December 21 — Hospital case presentation. Dr. S. J. Thannhauser.

Medical conferences will be resumed Tuesday, January 7, 1941.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, December 5, at 7:15 p.m., in the classroom of the nurses' residence. There will be a moving-picture presentation of the clinical and biological evaluation of Gonadogen.

INTERNATIONAL COLLEGE OF SURGEONS

There will be a cancer clinic of the International College of Surgeons, New England Division, at the Westfield State Sanatorium, on Tuesday, December 10, at 2 p.m.

PROGRAM

Address of welcome. Dr. George S. Foster, of Manchester, New Hampshire.

Cancer of the Lip: Operative technic illustrated by slides. Dr. Ernest M. Daland, of Boston. Discussion by Dr. Stephen A. Cobb, of Sanford, Maine.

Diaphragmatic Complications Secondary to Tumors. Dr. John W. Turner, of Springfield. Discussion by Dr. Thomas F. Broderick, of Boston.

Embryonal Tumors of the Ovary. Dr. Alfred M. Glickman, of Springfield. Discussion by Dr. Edward S. Brackett, of Providence, Rhode Island.

The Detection of Bone Metastases by Means Other than X-ray. Dr. Robert Fienberg, of Westfield. Discussion by Dr. R. Nelson Hatt, of Springfield.

The Treatment of Rectal Malignancies with Demonstration of Cases. Dr. Frank H. Baehr, of Springfield. Discussion by Dr. James A. Gettings, of New Haven, Connecticut.

The Lynch Operation for Rectal Cancer (motion pictures). Dr. Jerome M. Lynch, of New York City. Discussion by Dr. Adam P. Leighton, of Portland, Maine.

Bladder Malignancies. Dr. James A. Seaman, of Springfield. Discussion by Dr. George P. Cheney, of New London, Connecticut.

The End Result of Surgery in Breast Cancer. Dr. William S. Bainbridge, of New York City.

Physicians are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, December 1

Monday, December 2

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

Tuesday, December 3

*9–10 a.m. Case Study of Adrenal Deficiency in an Infant. Drs. F. C. McDonald and Nicholas Werthessen. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

Wednesday, December 4

New England Obstetrical and Gynecological Society.

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

2 p.m. New England Dermatological Society. Boston City Hospital.

*2–4 p.m. Jaundice. Drs. Soma Weiss and E. C. Cutler. Peter Bent Brigham Hospital.

Thursday, December 5

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

*9–10 a.m. Vascular Disease as Seen in the Ocular Fundi. Dr. Benjamin Sachs. Joseph H. Pratt Diagnostic Hospital.

7:15 p.m. New England Hospital for Women and Children. Monthly clinical conference and meeting of the staff.

Friday, December 6

*9–10 a.m. Some Aspects of the Aging Heart. Dr. H. B. Sprague. Joseph H. Pratt Diagnostic Hospital.

Saturday, December 7

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

December 3–21 — Joseph H. Pratt Diagnostic Hospital. Page 914.

December 4 — Wachusett Medical Society. Page 876, issue of November 21.

December 8–11 — American Academy of Dermatology and Syphilology. Page 831, issue of November 14.

December 10 — New England Society of Anesthesiology. Page 743, issue of October 31.

December 10 — Harvard Medical Society. Page 914.

December 10 — International College of Surgeons. Page 914.

December 12 — Pentucket Association of Physicians. Page 263, issue of August 15.

December 27–29 — National Convention of the Association of Medical Students, Boston.

January 4, 1941 — American Board of Obstetrics and Gynecology. Page 787, issue of November 7.

March 8 — American Board of Ophthalmology. Page 201, issue of August 1.

April 21–25 — American College of Physicians. Page 1065, issue of June 20.

May 21, 22 — Massachusetts Medical Society, Boston.

June 2–6 — American Medical Association. Cleveland, Ohio.

District Medical Societies

ESSEX SOUTH

December 4–May 14 — Page 831, issue of November 14.

January 8 — Visceral Pain and Its Relief. Dr. James C. White. Danvers State Hospital, Hathorne.

February 5 — Subject to be announced. Lynn Hospital.

March 5 — X-ray in Heart Disease. Dr. Merrill C. Sosman. Essex Sanatorium, Middleton.

April 2 — Pediatric Problems in General Practice. Dr. Joseph Garland. Addison Gilbert Hospital, Gloucester.

May 14 — Relation of the Doctor to the Law. Mr. Leland Powers. New Ocean House, Swampscott.

FRANKLIN

January 14.

March 11.

May 13.

Meetings will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

NORFOLK

January 28 — Carney Hospital.

February 25 — Medico-Legal meeting. 8:30 p.m. Hotel Puritan, Boston.

March 25 — To be announced.

May 8 — Censors' meeting. Hotel Puritan.

SUFFOLK

January 29 — Page 604, issue of October 10.

April 30 — Page 604, issue of October 10.

WORCESTER

December 11 — St. Vincent Hospital, Worcester.

January 8, 1941 — Worcester City Hospital, Worcester.

February 12 — Worcester State Hospital, Worcester.

March 12 — Memorial Hospital, Worcester.

April 9 — Hahnemann Hospital, Worcester.

Supper at 6:30 p.m. followed by a business meeting and scientific program.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Pioneer Doctor in Old Japan: The story of John C. Berry, M.D. By Katherine Fiske Berry. 8°, cloth, 247 pp., with 20 illustrations. New York: Fleming H. Revell Company, 1940. $2.50.

Laboratory Text in Pharmacology. By Robert P. Walton, professor of pharmacology, University of Mississippi School of Medicine. 8°, cloth, 85 pp. Philadelphia: J. B. Lippincott Company, 1940. $1.50.

The Diagnosis and Treatment of Cardiovascular Disease. Volumes I and II. Edited by William D. Stroud, B.S., M.D., professor of cardiology, University of Pennsylvania Graduate School of Medicine, and cardiologist to the Pennsylvania, Graduate, Bryn Mawr, Abington Memorial, St. Christopher's and Children's Heart hospitals. 4°, cloth; Volume I, 832 pp., with 163 illustrations, and Volume II, 855 pp., with 153 illustrations. Philadelphia: F. A. Davis Company, 1940. $18.00.

Obstetrics in General Practice. By J. P. Greenhill, B.S., M.D., professor of obstetrics and gynecology, Loyola University School of Medicine, Chicago, professor of gynecology, Cook County Graduate School of Medicine, and attending gynecologist, Cook County Hospital. 8°, cloth, 448 pp., with 112 illustrations. Chicago: Year Book Publishers, Inc., 1940. $3.50.

The Practice of Medicine. By Jonathan Campbell Meakins, M.D., LL.D., professor of medicine and director of the Department of Medicine, McGill University Faculty of Medicine, physician-in-chief, Royal Victoria Hospital, Montreal, formerly professor of therapeutics and clinical medicine, University of Edinburgh, fellow of the Royal Society of Edinburgh, fellow of the Royal Society of Canada, fellow of the Royal College of Physicians, London, fellow of the Royal College of Physicians, Edinburgh, honorary fellow of the Royal College of Surgeons, Edinburgh, and fellow of the Royal College of Physicians, Canada. Third edition. 4°, cloth, 1430 pp., with 562 illustrations, including 48 in color. St. Louis: C. V. Mosby Company, 1940. $10.00.

Office Urology, with a Section on Cystoscopy. By P. S. Pelouze, M.D., assistant professor of urology, University of Pennsylvania School of Medicine, consulting urologist, Delaware County Hospital, special consultant to United States Public Health Service, and member of Board of Directors, American Social Hygiene Association and American Neisserian Medical Society. 4°, cloth, 766 pp., with 443 illustrations, 19 in color. Philadelphia: W. B. Saunders Company, 1940. $10.00.

Advances in New York City's Health: Annual report of the Department of Health of the City of New York for 1939 with a review of developments from 1934–1939. John L. Rice, M.D., commissioner of health. New York: Department of Health, 1940. Complimentary.

Methods for Diagnostic Bacteriology: A complete guide for the isolation and identification of pathogenic bacteria for medical bacteriology laboratories. By Isabelle G. Schaub, A.B., assistant in bacteriology, Department of Pathology and Bacteriology, Johns Hopkins University School of Medicine, and M. Kathleen Foley, A.B., bacteriologist in charge of the Diagnostic Bacteriological Laboratory, Medical Clinic, Johns Hopkins Hospital, Baltimore. 8°, cloth, 313 pp. St. Louis: C. V. Mosby Company, 1940. $3.00.

Borrowed Children: A popular account of some evacuation problems and their remedies. By Mrs. St. Loe Strachey. With a foreword by Amabel Williams-Ellis. 12°, cloth, 149 pp. New York: Commonwealth Fund, 1940. 75 cents.

The Rockefeller Foundation, International Health Division: Annual report, 1939. 8°, paper, 230 pp., with 15 illustrations. New York: The Rockefeller Foundation, 1940.

Dr. Colwell's Daily Log for Physicians: A brief, simple, accurate financial record for the physician's desk. 4°, cloth. Champaign, Illinois: Colwell Publishing Company, 1940. $6.00.

BOOK REVIEWS

Frank Howard Lahey: Birthday volume, June 1, 1940. 8°, cloth, 466 pp., with 71 illustrations and 29 tables. Springfield, Illinois: Charles C Thomas, 1940.

To commemorate Dr. Frank H. Lahey's sixtieth birthday, his associates, friends and others have issued a volume of papers, largely surgical, covering a varied field. Since there is no index, the papers themselves will be of little value to the medical profession, and few librarians will find them of sufficient value or importance to catalogue the authors and titles separately. This is indeed unfortunate, for tucked away in volumes of this sort are rare gems, such, for example, as one by Ray Lyman Wilbur on "Mental Laundries," which is an essay on individual practice at its best.

In general, the work of the Lahey Clinic is reflected in the contributions to this volume. A large number deal with the surgery of the gastrointestinal tract. No paper describes the history of the clinic itself, except one about the neurosurgical service. One misses, too, any adequate report on Dr. Lahey and his important relations to the medical profession as a whole. The volume, therefore, in spite of being a splendid tribute, richly deserved, to one of the leaders of American medicine, is somewhat of a disappointment to the general reader.

The format is pleasing; a photograph of Dr. Lahey serves as a frontispiece, and there are numerous illustrations in association with the papers. References to the literature accompany most of the contributions.

Physiological Optics. By W. D. Zoethout, Ph.D. Third edition. 8°, cloth, 406 pp., with 214 illustrations. Chicago: Professional Press, 1939. $5.00.

Of the several modern texts on physiologic optics, this book is probably the most appropriate for a cursory review of the subject. The third edition presents the orthodox material in an orthodox way. In avoiding controversy, it unfortunately gives the unwarranted impression of finality, but perhaps this is inevitable in view of the book's brevity. On the whole, it is a very readable introduction to the subject.

The Dream World: A survey of the history and mystery of dreams. R. L. Mégroz. 8°, cloth, 319 pp. New York: E. P. Dutton & Company, Inc., 1939. $2.50.

This volume is an anthology of dreams and of dream literature, and at the same time, a summary of theories and historical material. It gives an account of the dreams and dream cults of savage and civilized people and of the popular literature on dreams from ancient to modern times. It demonstrates by quotation how this literature has often anticipated modern theories, and also how it emphasizes supernormal knowledge and telepathic communication.

It is well known, even outside the scientific literature of dreams, that the dream pursues the dreamer's waking interests. For instance, the Queen Mab speech in *Romeo and Juliet* or Petronius's statement that "each man makes dreams for himself" both show that dreams are wish-fulfillments. It is interesting, also, as the author points out, that Lincoln, who was liable to depressed moods and had frequent presentiments of a violent death, had a momentary anxiety-dream of his own assassination.

The author believes that the mystery of dreaming includes supernormal knowledge and extrasensory perception and emphasizes that dreams have become too much bound with psychotherapy and the analysis of unconscious motives. Freud's theory of dreams is referred to as "materialism in psychology," in spite of the fact that Freud reiterates that the dream is a subjective psychic production. In fact, the last chapter of Freud's *The Interpretation of Dreams* is entitled "The Psychology of Dream Activities." As for dreaming the future, careful analyses have shown that the dream originates from the past and touches on the future only by representing a wish as fulfilled; it is therefore in no sense "prophetic." There is no evidence, according to the scientific literature of dreams, that they bear any relation to telepathy.

As an anthology the volume is useful, but it does not attempt to solve any of the abstruse problems of dream psychology.